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THE RENAL COMPLICATIONS OF LEUKEMIA*

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ALTHOUGH many authors[1-6] have commented on the frequency of leukemic infiltration of the kidneys at some time during the course of the disease, and others[1, 7-11] have reported the frequency of renal stone and the rare complication of gout,[1, 10-15] only a few[7, 8, 16, 17] have suggested taking advantage of these facts in planning x-ray treatment. This is usually of little importance, since all present-day methods of treatment in leukemia are merely delaying rearguard actions. However, in an occasional case this knowledge is of benefit to the patient, so that it has seemed worthwhile to call attention once again to these not infrequent complications of a practically invariably fatal disease.

Mach[6] reported a case of acute myeloid leukemia that at onset showed peripheral edema and urine containing albumin, casts and red and white cells in the sediment, which led to an initial erroneous diagnosis of acute nephritis. There was no azotemia or hypertension. A post-mortem examination showed bilateral leukemic infiltration of the kidneys.

Naegeli[1] has commented on the frequency of "chronic nephritis" in chronic lymphatic leukemia. He has also pointed out the frequency of uric acid stones but the rarity of gout in myeloid leukemia. He, as most other authors on this subject,[1, 4, 10-15] thinks that the occurrence of gout in leukemia is probably pure coincidence, or that at most the leukemia may be regarded as a contributory factor in a patient with a constitutional predisposition to gout. Bedrna and Polcak[9] have reported 2 cases of acute ureteral obstruction by uric acid stones complicated by leukemia,—in one myeloid and in the other lymphatic,—in both of which the complication developed shortly following x-ray treatment. In both cases the stones were removed by ureteral catheterization and the patients were relieved of this acute complication.

Jugenburg and Tschotschia[7] have reported detailed studies of the uric acid metabolism in patients with leukemia undergoing x-ray treatment. They emphasize the danger of renal failure in these cases, due either to actual leukemic infiltration of renal tissue or to the overloading of kidneys already involved in nonleukemic degenerative lesions, and forced to excrete large amounts of uric acid consequent to the x-ray destruction of high numbers of immature white cells.

One of us (D. M.[8]) has also reported 3 cases of leukemia where renal failure was apparently precipitated by x-ray therapy.

A case of chronic lymphatic leukemia was reported by Cabot[18] in which the patient died seventeen days after the institution of x-ray therapy. The urine showed red and white cells in the sediment, and vomiting began after the first x-ray treatment. The post-mortem examination showed extensive leukemic infiltrations in both kidneys. The course was consistent with death from uremia, but unfortunately no blood-nonprotein-nitrogen or blood-urea studies had been done during life.

In the records of the Pondville Hospital there have been 18 autopsied cases of leukemia during the last nine years. Ten patients had impaired renal function before death. Of these, 4 actually died in uremia (3 of them having nephrolithiasis), 2 others had nephrolithiasis, and 4 had extensive gross and microscopic leukemic infiltration of the kidneys.

The following 3 cases (2 from the Pondville Hospital and 1 from another hospital) are reported in detail in order to emphasize the clinical importance of renal complications in leukemia. Brief abstracts of the 8 other cases from the Pondville Hospital are given at the end of this paper.

CASE REPORTS

CASE 1. H. A. (P.H. 15736), a 61-year-old man, was admitted to the hospital on June 8, 1939, with a diagnosis

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of chronic myeloid leukemia, chronic infectious arthritis and carcinoma of the conjunctiva of the right eye. He had been perfectly well until January, 1937, when one night he suddenly developed burning and itching of the skin of both feet and ankles, lasting about an hour and followed by mild aching in both feet. The next morning both ankles were acutely painful, red, hot, and swollen to about twice their natural size. This initial attack lasted for 2 weeks. From then on there were recurrent attacks of the same type of arthritis, involving first one joint and then another, until it became more or less continuous. The joints most affected were the ankles, knees, right elbow and right wrist. During periods of freedom from pain the patient was able to walk about quite comfortably without crutches or cane. The attacks were never associated with chills, fever or sore throat, and were prone to begin suddenly at night and subside gradually over a period of several days to weeks.

Six months after the first episode of joint pain, the patient had a sudden attack of severe left-sided abdominal cramps, not radiating to the groin or back and not associated with nausea or vomiting. He was admitted to a hospital in another state, where he was discovered to have an enormously enlarged spleen, and after extensive blood and x-ray studies was told that he had an incurable disease for which nothing could be done. However, he felt in his usual excellent health except for the recurrent attacks of joint pain, and so left the hospital against advice. In January, 1939, 6 months before coming to the Pondville Hospital, the patient entered another hospital, where diagnoses of infectious arthritis and myeloid leukemia were made and he was given a course of sixteen x-ray treatments of the spleen without any noticeable effect on the joint pains, which were the only symptoms that bothered him. In May, 1939, the patient was observed to have a white spot on the scleral conjunctiva of the right eye. This grew slowly. A biopsy specimen was diagnosed as epidermoid carcinoma, and he was therefore referred to the Pondville Hospital for x-ray treatment. When admitted he complained only of pain in the joints.

The past history included an episode of profuse bleeding from the gums for 3 days after tooth extractions in 1929, and a similar episode in 1937. Both the parents lived to old age, dying of natural causes. Neither suffered from gout or arthritis.

Physical examination showed a well-developed, fairly well-nourished, plethoric-looking man of 61. Many telangiectases were scattered over the face. There were numerous small tophi in the lobes of both ears, but none were palpable around any of the joints. In the right eye extending over the limbus of the cornea was a small, whitish lesion of the conjunctiva, slightly elevated above the surrounding sclera. The oral mucous membranes were a deep red. There were four remaining badly infected teeth in the lower jaw. The heart and lungs were essentially normal. The blood pressure was 132/85. The spleen was enormously enlarged and extended 3 cm. below the umbilicus and 1.5 cm. to the right of the midline. The liver was also enlarged and extended about 8 cm. below the costal margin. There was a large easily reducible left inguinal hernia, and a smaller one on the right. All the joints appeared to be normal except for the right knee, where there was redness, swelling, heat and fluctuation over the prepatellar bursa. Both knees were painful on active or passive motion.

The red-cell count was 5,200,000 and the hemoglobin 93 per cent (Sahli). The white-cell count was 31,400, with 91 per cent polymorphonuclear leukocytes, 2 per cent monocytes, 1 per cent eosinophils, 2 per cent basophils, 2 per cent metamyelocytes and 2 per cent stem cells. The urine was acid, with a specific gravity of 1.020, no albumin and no sugar. The sediment contained innumerable white cells and contained 25 red cells per high-power field. A blood Hinton test was negative. The nonprotein nitrogen was 53 mg., the blood uric acid 8.5 mg., and the creatinine 1.74 mg. per 100 cc. A phenolsulfonephthalein test showed 25 per cent excretion in the 1st hour and 20 per cent in the 2nd. The basal metabolic rate was +70 per cent. X-ray films of the joints showed no changes characteristic of gout, but microscopic examination of the material obtained from a tophus in the ear lobe showed sodium urate crystals.

Diagnoses of gout, myeloid leukemia and carcinoma of the conjunctiva were made.

The patient remained under practically constant observation from this time until his death on October 31, 1940, approximately 1 year and 5 months later, or 3½ years after the discovery of his splenomegaly.

The conjunctival carcinoma responded to x-ray therapy and was cured in about 1 month's time. The patient's slow downward course was punctuated by increasingly frequent attacks of gout, which responded less and less to colchicine, cinchophen and a diet low in fat and purines. The renal function, which was slightly impaired when he was first studied, diminished steadily. One year after admission phenolsulfonephthalein excretion had fallen to 5 per cent in 2 hours, though the nonprotein nitrogen still remained around 50 mg. per 100 cc.

Two months before death the white-cell count reached 56,000, and inasmuch as the patient had never reacted well to x-ray therapy, a trial of Fowler's solution was made. In the week following the institution of this treatment the white-cell count dropped to 30,000, but the nonprotein nitrogen rose steadily to 71 mg. per 100 cc. As the patient was clinically on the verge of uremia, the potassium arsenite was stopped and the fluid intake was increased. The nonprotein nitrogen then dropped to 35 mg., but again rose slowly to 63 mg. on the day of death. There was occasional gross hematuria, and almost all the urinary sediments examined had microscopically demonstrable red cells, though there was no clinically recognizable episode of renal colic.

The red-cell count remained between 4,000,000 and 6,000,000 for the first 4 months of observation but then began to fall, and at the time of death was 1,720,000, with a hemoglobin of 20 per cent (Sahli). The white-cell count varied from 12,000 to 60,000, but no differential count showed more than 15 per cent myelocytes.

X-ray treatment was given to the kidneys in the hope of improving the renal function, but no significant benefit could be demonstrated. A course of x-ray treatments was twice given to the spleen, with only slight effect on the white-cell count, and each time with a severe exacerbation of the gout. However, since the patient had had so many attacks of gout and the x-ray treatments were spread out over a week's time, it is impossible to be sure that the latter increased the gout. At all events, the patient was not helped by the x-ray treatment. The trial of Fowler's solution, as mentioned above, resulted in a rapid temporary drop of the white-cell count but coincided with an alarming rise of the nonprotein nitrogen, so that this too was discontinued. The patient finally died with extreme cachexia, profound anemia and chronic renal insufficiency.

Autopsy. The spleen weighed 1360 gm., and the liver 2475 gm. The kidneys were of normal size, weighing 110 gm. each. There was a large stone in the pelvis of the right kidney, and several small ones in the calyxes on the right. There was also a small stone in the lower end of the right ureter just proximal to the opening into the bladder. Microscopic examination of the kidneys showed relatively normal findings except for the presence of masses of leukocytes and myelocytes in the blood vessels and a small area of leukemic infiltration in the cortex. The bone marrow showed the characteristic picture of chronic myeloid leukemia.

In brief, this patient had chronic myeloid leukemia and gout. During his last 4 years of life practically all his symptoms were due to gout, although renal insufficiency was a factor in the last year and a half. An incidental finding was a carcinoma of the conjunctiva of the right eye that was cured by radiation therapy. At autopsy the diagnosis of leukemia was confirmed and multiple renal calculi (pelvic and ureteral) were found that doubtless were a contributory if not the main cause of his impaired renal function. The similarity of this case to the one reported by Reifenstein[14] is striking.

Case 2. E. M. H. (P.H. 19588), a 28-year-old, married woman, was admitted to the hospital on November 9, 1941, for x-ray treatment on the basis of a previous diagnosis of lymphosarcoma. She had been perfectly well until 4 months previously, when she began to have marked frequency of urination during the day and had to void twice during the night. This continued for 2 months but was not associated with any other symptoms. She felt perfectly well and the frequency gradually disappeared. Six weeks prior to entry she began to have moderately severe lower abdominal pain, chiefly on the left but sometimes in the right groin. The pain came on gradually and lasted for several hours, and was apt to be worse at night. It was sometimes knifelike and severe enough to double her up, but at other times it was merely a dull ache. There was some loss of appetite, and mild indigestion. Occasionally the patient was feverish and once or twice had profuse night sweats. At about the time the abdominal pain began she first noticed some painless swellings in her neck, and subsequently more and more lumps appeared in both sides of the neck and behind the ears. She had also noticed a tendency to bruise more easily than usual in the preceding few weeks, and had been menstruating for 10 days at the time of admission. There had been gradually increasing dyspnea for the preceding 2 months. She had been seen in another hospital, where a lymph node had been removed from the neck for diagnostic purposes. A diagnosis of lymphosarcoma had been made on the section, so that she was referred to the Pondville Hospital for x-ray therapy.

The past history included osteomyelitis of the left leg at 7 and removal of the appendix and an ovarian cyst at 24.

Physical examination showed a well-developed, pale, obese woman with masses of discrete firm nodes in both sides of the neck. Enlarged nodes could also be felt in front of and behind both ears, in both axillas and in both groins. The nodes were firm and discrete and varied in diameter from 0.5 to 2.0 cm. There were purpuric spots on the skin of the chest and left arm. The gums and mucous membranes were pale but showed no hemorrhages. The heart and lungs were within normal limits. The blood pressure was 160/85. The abdomen was distended, tympanitic, and tender in both lower quadrants. The spleen was felt two fingerbreadths below the costal margin. The legs were obese but there was no pitting edema.

The red-cell count was 1,700,000 and the hemoglobin 30 per cent (Sahli). The white-cell count was 4000, with 40 per cent polymorphonuclear leukocytes, 21 per cent lymphocytes, 1 per cent basophils, 4 per cent metamyelocytes and 32 per cent extremely large immature cells, thought to be lymphoblasts. The red cells showed marked variation in size and shape, and occasional nucleated red cells were seen. A blood Hinton test was negative. The urine showed a specific gravity of 1.015, the slightest possible trace of albumin and no sugar. The sediment contained occasional red cells and 8 white cells per high-power field, with occasional clumps of the latter. The blood nonprotein nitrogen was 20 mg. per 100 cc.

A diagnosis of acute lymphatic leukemia was made. The prognosis was considered extremely grave, but the patient was given repeated transfusions (3500 cc. of blood in seven transfusions), and as she continued to bleed from the uterus was given radiation therapy to the pelvis in the hope of stopping the bleeding.

On November 27, 18 days after admission, a generalized convulsion occurred and the blood pressure was 240/130. The urine showed a large trace of albumin and many red and white cells in the sediment. The blood nonprotein nitrogen was 66 mg. per 100 cc. The patient was drowsy, there was pitting edema of the legs and face, and the eyes were puffy. The nonprotein nitrogen continued to rise, reaching 80 mg. on December 1. Because of the possibility that these manifestations of acute nephritis were due to leukemic renal infiltration, a course of x-ray treatments was given to the kidneys. This was followed by improvement, with a gradual drop of the nonprotein nitrogen to 30 mg. on December 13. The facial edema gradually cleared, but the edema of the legs remained about the same. The blood pressure had dropped to 170/120 by November 30 and was 180/105 on December 2, when another series of x-ray treatments was begun to the region of the kidneys. There was a slight further drop to 170/110 on December 4 and to 170/90 on December 15, and finally to 110/65 on December 16, the day of death. Thoracenteses were done on December 6 and 13, with the removal of 1800 cc. of clear, yellow fluid each time. In spite of the apparent improvement of kidney function the patient failed rapidly and died about 5 weeks after admission. During these weeks the hemoglobin had varied from 30 to 53 per cent (Sahli) and the white-cell count from 4000 to 2000. The large, immature white cells varied from 2 to 36 per cent.

Autopsy. There were bilateral pleural effusions, enlargement of the spleen (weight 350 gm.) and of the liver (weight 1900 gm.) and a large retroperitoneal tumor. Around the aorta, in both the thoracic and abdominal portions, there were many enlarged lymph nodes, and in addition there was a diffuse infiltration of the adjacent areolar tissue by yellowish, firm tissue similar in appearance to that of the lymph nodes. This tissue was quite dense and was hard to dissect from the vertebral bodies. Retroperitoneally, particularly in the lower left portion, this para-aortic tumor was extensive, completely surround-

ing the great vessels, the renal vessels, both ureters, the adrenal glands and the pancreas, and infiltrating and practically surrounding the pelvic organs. The tumor also extended along the femoral vessels into both legs. The tracheobronchial and mesenteric lymph nodes showed only slight enlargement. No ante-mortem thrombi were found in any of the compressed blood vessels. The kidneys were somewhat enlarged, the right kidney weighing 250 gm. and the left 180 gm., and there were multiple small urate stones in the right kidney, pelvis and calyxes. On microscopic examination the kidney sections showed extraordinarily few abnormalities. A section from the left kidney showed slight interstitial fibrosis and tubular dilatation, which were not present on the right. Sections from both kidneys showed normal glomeruli, but in the convoluted tubules there were epithelial swelling and granularity and some nuclear pyknosis. Many tubules contained amorphous material, and a few contained granular casts. The peripelvic tissues showed neoplastic cellular infiltration, but the kidney parenchyma did not. Histologic examination of the tumor masses showed a neoplasm that was diagnosed as Hodgkin's sarcoma by Dr. Frederic Parker, Jr., of the Mallory Institute of Pathology. In addition, the spleen and bone marrow showed an infiltration of cells without the formation of tumor nodules.

In retrospect one cannot be certain of the cause of this patient's episode which simulated acute nephritis. She did have multiple renal calculi on the right, and both ureters and renal arteries and veins were imbedded in tumor tissue. The kidneys themselves showed practically no infiltration with tumor, though they had received x-ray treatments, followed by a temporary improvement of renal function. The most likely explanation seems to be impairment of renal function through mechanical obstruction of the ureters and renal blood vessels by extrarenal tumor, but renal calculi on the right may also have been a contributory factor. In summary, this patient with acute leukemia had an episode simulating acute nephritis with edema, hypertension, convulsions and nitrogen retention, which subsided following x-ray therapy to the kidneys. At autopsy she was found to have multiple renal calculi, and both ureters and renal arteries and veins were imbedded in tumor tissue that was diagnosed as Hodgkin's sarcoma.

CASE 3. S. C. (C.H. 9068),* a 68-year-old woman, came under medical observation in October, 1941, because of increasing dyspnea, fatigability, weakness and weight loss of 1 year's duration. She was found to have signs suggestive of early cardiac decompensation and was put to bed and digitalized. She soon became nauseated, so that the digitalis was stopped. Two weeks after being put to bed she developed phlebitis, which gradually spread in the next 5 weeks to involve both legs from groin to ankle. Her appetite was poor; she felt weak, became increasingly pale and ran a daily temperature of about 100°F. A specimen of urine showed a large amount of albumin, but in a second one examined several weeks later the albumin was within normal limits. The patient had no cough or dyspnea while lying in bed, but because of her rapid downhill course with increasing pallor and weakness she was sent to the Cambridge Hospital.

On admission, 7 weeks after her first visit to a physician, the patient presented a picture of marked pallor and debility. The heart was enlarged, the apex impulse being in the anterior axillary line. There were occasional premature beats, and a systolic murmur was heard all over the precordium. The heart rate was 100, and the blood pressure 130/40. The lungs showed dullness at the left base, with bronchial breath sounds and coarse rales. The liver was felt one fingerbreadth below the costal margin, and the tip of the spleen was felt 1 cm. below the left costal margin. There was gross edema of the left leg from the groin to the toes, with induration and tenderness in the popliteal space. The right leg was slightly swollen above the knee and considerably swollen below it.

The red-cell count was 2,560,000 and the hemoglobin 42 per cent (Sahli). The white-cell count was 409,600, with 32 per cent polymorphonuclear leukocytes, 14 per cent band forms, 2 per cent lymphocytes, 34 per cent myelocytes, 12 per cent metamyelocytes, 4 per cent basophils and 3 per cent myeloblasts. The urine was yellow and cloudy, with a specific gravity of 1.006, a very slight trace of albumin and no sugar. The sediment contained from 10 to 20 white cells per high-power field and numerous hyaline casts. The blood nonprotein nitrogen was 250 mg. per 100 cc. A blood Hinton test was negative. X-ray examination of the chest showed a small amount of fluid and some pneumonia at the left base. A second white-cell count the day after admission was 590,000. The patient had increasing dyspnea for 3 days and died suddenly on the 4th day.

Autopsy. In addition to the usual findings in myeloid leukemia, there was thrombosis of both femoral and iliac veins, as well as multiple small pulmonary emboli. There was a small patch of bronchopneumonia. The heart weighed 290 gm., and showed mild arteriosclerosis and arteriolar sclerosis and a small mural thrombus in the apex of the right ventricle. The kidneys were of considerable interest in view of the high nonprotein nitrogen (250 mg. per 100 cc.) 3 days before death. They weighed 160 gm. each and were grossly normal. There were no stones in the pelves or ureters. Microscopic examination, however, showed considerable arteriosclerosis of the renal arteries and arterioles, and almost complete stasis throughout the vascular channels, beginning in the glomeruli, continuing in the intertubular capillary system and being most obvious in the large, dilated veins. Most of the glomeruli were intact, and the capsules were not thickened. Many showed dilatation of the afferent arterioles and of the glomerular-tuft capillaries, which were distended with blood cells, mostly primitive white cells, some of which were undergoing mitosis. There were foci of leukemic cells within the interstitial tissue, especially around the large veins, but they apparently played little or no role in mechanical obstruction of the tubules. It was thought that the uremia could be explained on the basis of a failing circulation with stasis and obstruction of the glomerular capillaries.

In brief, this elderly woman with leukemia, thrombophlebitis of both iliac and femoral veins and multiple small pulmonary infarcts died in uremia. Her renal insufficiency was due in part to circula-

*Reported through the courtesy of Dr. Gordon A. Saunders, of Arlington.

tory failure and anemia and in part to blocking of the glomerular capillaries with leukemic cells.

Summary

Attention is once again called to the frequency of renal failure in leukemia. The causes of this complication are nephrolithiasis, infiltrative leukemic lesions of the kidneys, obstruction of renal blood vessels or ureters by leukemic tissue, or finally nonleukemic degenerative lesions of the kidneys. The rare occurrence of gout in cases of leukemia is noted. Three cases exemplifying these complications are reported.

It is hoped that knowledge of these complications may occasionally be of help in planning the treatment of this incurable disease.

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Brief Abstracts of the Other Cases at the Pondville Hospital

Case 4. E. M. S. (P.H. 11306, previously reported in detail[8]), a 65-year-old woman, who had had a mass in the left upper quadrant of the abdomen for several years, a mass in the left breast for 8 years, and had recently lost 75 pounds, was found to have a small, hard, nodular, ulcerated mass in the left breast, a palpable hard lymph node in the left axilla and an enormously enlarged spleen. The blood picture was characteristic of chronic myeloid leukemia, with a white-cell count of 380,000 and a blood nonprotein nitrogen of 65 mg. per 100 cc. The urine showed a specific gravity of 1.016 and a trace of albumin, with red and white cells in the sediment.

Following x-ray therapy the white-cell count dropped to 25,100, but the patient died in uremia with a nonprotein nitrogen of 188 mg. per 100 cc.

Autopsy showed chronic myeloid leukemia, and carcinoma of the left breast with axillary metastases. The kidneys showed some grayish-white, inspissated material in the right pelvis, and microscopically there were foci of lymphocytic infiltration, hyalinized glomeruli, atrophied tubules and subintimal thickening in the large blood vessels. In the pelvic fat in one section there was a mass of loose connective tissue in which were collections of leukemic cells.

Case 5. W. C. (P.H. 12612), a 71-year-old man, was admitted because of loss of appetite, a weight loss of 25 pounds and diarrhea of 3 months' duration. There had been an eruption on the back of both hands for 6 weeks. On examination he was found to have skin lesions on the backs of both hands and of the right forearm consistent with pellagra. There were large masses of soft lymph nodes in both axillas and inguinal regions and an enormously enlarged spleen. The blood showed the characteristic picture of chronic lymphatic leukemia. The white-cell count was 199,000, with 97 per cent lymphocytes, and the red-cell count was 1,730,000, with a hemoglobin of 37 per cent (Sahli). The nonprotein nitrogen was 31 mg. per 100 cc. and the urine sediment showed red and white cells and occasional hyaline casts.

X-ray treatment was given to the spleen, with a drop in the white-cell count to 112,600 but without much clinical benefit. Six months later because of increasing dyspnea and weakness the patient was readmitted and died 8 days later. Shortly before death the white-cell count was 167,000, with 98 per cent small lymphocytes, and the red-cell count was 1,400,000, with a hemoglobin of 25 mg. (Sahli).

Autopsy revealed the usual findings of chronic lymphatic leukemia. The kidneys showed gross and microscopic scattered areas of tumor infiltration.

Case 6. A. MacD. (P.H. 12941, previously reported in detail[8]), a 56-year-old man, was admitted with a history of increasing weakness, pallor and a weight loss of 30 pounds in 3 years. He was found to have an enormously enlarged spleen, and the blood findings were those of chronic myeloid leukemia, with a white-cell count of 237,500, a red-cell count of 2,940,000 and a hemoglobin of 54 per cent (Sahli). A phenolsulfonephthalein test showed 15 per cent excretion in the 1st hour and 15 per cent in the 2nd.

X-ray treatments were given to the spleen from time to time during the next 21 months, with considerable benefit. On the 4th hospital admission the spleen was enormously enlarged, the white-cell count was 210,000, and the hemoglobin was 60 per cent. The blood nonprotein was 47 mg. per 100 cc. Following x-ray treatment the white-cell count fell steadily to 3800 in 1 month. The blood nonprotein nitrogen, however, rose steadily to 244 mg. and the patient died in uremia.

Autopsy showed the usual findings of chronic myeloid leukemia. The kidneys were of particular interest. Both contained multiple uric acid and urate calculi in the calyxes, and the upper portion of the ureter was packed with gravel. Sections from the right kidney showed evidence of an active pyelonephritis.

Case 7. H. S. E. (P.H. 15613), a 54-year-old man, was admitted because of enlarged painless lymph nodes of 1 year's duration. He was found to have tremendously enlarged cervical, supraclavicular axillary and inguinal nodes. The liver and spleen were not felt. X-ray films

showed enlarged mediastinal nodes. The white-cell count was 3000, with 50 per cent polymorphonuclear leukocytes, 49 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils, but with a later lymphocyte percentage of 80 when the total cell count was 3400. The red-cell count was 3,110,000, with a hemoglobin of 52 per cent (Sahli). The nonprotein nitrogen was 52 mg., and the blood uric acid 8 mg. per 100 cc. A phenolsulfonephthalein test showed 45 per cent excretion in 2 hours, and the basal metabolic rate was +80 per cent. The urine showed a slight trace of albumin, and the sediment contained a few finely granular and coarsely granular casts and 10 white cells per high-power field.

X-ray therapy was given to both kidneys and to the right side of the neck. The nonprotein nitrogen dropped to 39 mg. and the blood uric acid to 4 mg. per 100 cc. The white-cell count dropped to 1800, with 60 per cent lymphocytes. The patient continued to feel well, but because of his leukopenia he was transfused. The next day he developed pulmonary edema and died.

Autopsy showed the changes of chronic lymphatic leukemia and of septicemia. The kidneys contained numerous small foci of lymphocytes scattered irregularly throughout, although slightly commoner in the cortex. There were no stones.

Case 8. F. S. (P.H. 16077), a 37-year-old man, was admitted because of multiple hemorrhagic tumors of the skin of 9 weeks' duration. He had lost between 15 and 20 pounds in weight and had rapidly become worse in spite of x-ray treatment. The entire body had a purplish-red hue. Scattered over the neck, chest and all four extremities were numerous purplish-red, hemorrhagic, soft tumor nodules, imbedded in the skin and freely movable over the underlying structures. These varied in diameter from 1 to 8 cm. There were firm, enlarged lymph nodes in the neck, axillas and groins, which were matted together. There was marked edema of both legs, the abdominal wall, penis and scrotum. Almost the entire skin of the body appeared to be infiltrated with tumor and had a thick, leathery feeling. Many places were ulcerated and weeping. There was a marked gingivitis involving both upper and lower gums, which appeared hyperplastic and hemorrhagic. There were many large and small submucosal hemorrhages. The spleen and liver could not be felt. The white-cell count was 10,400, with 66 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes, 4 per cent monocytes, 1 per cent myelocytes and 2 per cent nucleated red cells. The red-cell count was 2,250,000, with a hemoglobin of 35 per cent (Sahli). Three days later the white-cell count was 5900, with 79 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes, 1 per cent myelocytes and 7 per cent nucleated red cells. The nonprotein nitrogen was 53 mg. per 100 cc. on entry but rose to 81 mg. 2 days later. The urine showed only the slightest possible trace of albumin, and the sediment contained 1 red cell and 1 white cell per high-power field. The patient went rapidly downhill and died 5 days after admission.

Autopsy showed extensive infiltration of practically every organ of the body with lymphoblasts. The kidneys showed a heavy subcapsular, periglomerular and perivascular tumor-cell infiltration involving a large proportion of the cortical areas but almost absent in the medullas.

Case 9. M. J. (P.H. 16198), a 71-year-old man, was admitted because of generalized lymphadenopathy, hepatomegaly and splenomegaly of 1 month's duration. He was semicomatose on admission and died 5 days later. On admission the nonprotein nitrogen was 102 mg. per cent, and the urine essentially normal. The white-cell count was 18,300, with 78 per cent polymorphonuclear leukocytes, 3 per cent lymphocytes, 5 per cent monocytes, 8 per cent metamyelocytes, 2 per cent hemohistioblasts and 4 per cent hemocytoblasts. The red-cell count was 4,180,000, with a hemoglobin of 83 per cent (Sahli).

Autopsy showed an acute stem-cell leukemia. The kidneys showed minute foci of as well as diffuse infiltration with tumor cells, most marked in the cortices.

Case 10. E. G. (P.H. 16952), a 76-year-old woman, was admitted because of vaginal bleeding for 2 weeks. She was found to have an extensive carcinoma of the cervix. Blood studies, however, also showed the presence of an acute myeloid leukemia. The white-cell count was 99,700, with 1 per cent polymorphonuclear leukocytes, 1 per cent lymphocytes, 2 per cent myelocytes, 1 per cent promyelocytes, 87 per cent myeloblasts and 8 per cent hemocytoblasts. The red-cell count was 2,500,000, with a hemoglobin of 50 per cent (Sahli). The blood nonprotein nitrogen was 32 mg. per 100 cc. The urine showed a moderate amount of albumin, and the sediment contained 15 red cells and 50 white cells per high-power field. In spite of x-ray treatment the patient died 23 days after admission.

Autopsy showed advanced carcinoma of the cervix, with extension to the vaginal wall and broad ligaments, metastatic involvement of the right parailiac and paraaortic lymph nodes and metastases to the lungs. There were also the characteristic changes of acute myeloid leukemia. The kidneys showed a generalized intracapsular and perivascular infiltration with leukemic cells, as well as a patchy infiltration of the interstitial tissues, most marked in the cortices and in the peripelvic fat.

Case 11. J. H. G. (P.H. 17640), a 75-year-old man, was admitted because of vomiting of 12 weeks' duration. He had received x-ray therapy at another hospital because of a blood picture of lymphatic leukemia. There were scattered petechiae under the tongue and in the skin over the chest. The spleen and liver were both considerably enlarged. There were no significantly enlarged peripheral lymph nodes. The white-cell count was 9400, with 26 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes and 68 per cent lymphoblasts. The red-cell count was 9400, with a hemoglobin of 25 per cent (Sahli). The blood nonprotein nitrogen was 61 mg., and the blood uric acid 7.1 mg. per 100 cc. The urine contained a very slight trace of albumin, with 5 red cells per high-power field in the sediment. The patient became rapidly weaker, had bloody and tarry stools and developed additional cutaneous hemorrhages. He died 23 days after admission.

Autopsy showed the characteristic findings of lymphatic leukemia. In the left kidney there were several small calculi in the calyxes, and there was a large stone in the upper portion of the left ureter. Microscopic examination showed several small scars of old infarcts and a few foci of tumor cells, but the latter were most numerous in the peripelvic fat.

RENAL HYPERTENSION

A Review of Its Status, Including the Report of a Case of Hypertension Relieved after Nephrectomy

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SINCE Goldblatt's[1] publication in 1934, there has been widespread interest in the relation of the kidneys to hypertension. This has been manifested by reports of occasional cases of hypertension associated with unilateral renal disease in which the blood pressure was lowered following the removal of the offending kidney. The number of such reports has not been great, but some of the cases are so clear that there is no doubt of their validity.[2-15] There have also appeared several surveys of large numbers of hypertensive patients in which attempts have been made to classify the etiology of the disease. Although these reports have shown the presence of many types of renal disease in some cases of hypertension, and a higher incidence of hypertension in patients with renal disease than in those without, more precise correlations have been generally disappointing.[16-21] It is the purpose of this communication to review certain data with a bearing on this subject.

EXPERIMENTAL PHYSIOLOGY

Although Tigerstedt and Bergman[22] in 1898 isolated a vasopressor substance of renal origin, which they named "renin," and Janeway[23] subsequently succeeded in producing occasional hypertensive dogs by renal surgery, Cash[24] in 1924 was the first able to produce experimental hypertension consistently. His technic included excision of renal tissue and ligation of the renal vessels. His experiments were numerous, were carefully correlated, and included tests of renal function. His conclusions were consistent with subsequent experimental surgery and study of renal extracts. The Cash preparation is symbolized in Figure 1*C*. Cash concluded, first, that reduction of renal tissue by excision and by ligation of the renal vessels was followed under certain circumstances and in most cases by a rise of both systolic and diastolic blood pressures and in all cases by a rise in diastolic pressure averaging 27 mm.; that the required conditions were that 50 per cent of the kidney substance be removed and that the portion deprived of its circulation remain in situ; that necrosis alone or excision of one kidney alone produced no change in blood pressure; that after hypertension reached its peak in four or five days it tended to return to normal, the rate of return being proportional to the amount of good tissue left; and that after removing 25 to 85 per cent of the renal tissue no retention of nonprotein nitrogen occurred, whereas dye excretion was impaired after 50 per cent of the kidney tissue had been removed.

Although Cash's monumental work established the framework for the subsequent understanding of the action of renal extracts, it was Goldblatt[1] who precipitated a wide interest in that study. He found that sudden clamping of both renal arteries produced marked hypertension with uremia, a condition that he compared to malignant hypertension in man (Fig. 1*E*). Less severe bilateral clamping produced sustained elevation of blood pressure with prolonged life but no nitrogen retention and only occasional impairment of the urea clearance (Fig. 1*D*). Gradually increased clamping, however, produced very little change in blood pressure, a finding that Goldblatt attributed to the development of collateral capsular circulation. He also showed that experimental renal hypertension is independent of the adrenal glands or of the blood concentration of guanidine, and Page[25] subsequently showed that it is independent of the afferent nerves of the kidney.

Other surgical methods of producing hypertension also exist. Page,[25, 26] in attempting to find a method of preventing collateral capsular circulation, wrapped dogs' kidneys in cellophane (Fig. 1*G*). The animals became hypertensive. The cellophane broke down into a fibrocollagenous hull that stimulated proliferation and led to perinephritis. Harrison, Mason, Resnick and Rainey[27] found that bilateral clamping of the ureters generally produced hypertension with uremia (Fig. 1*F*), whereas bilateral nephrectomy resulted in uremia without hypertension (Fig. 1*B*).

The fact that certain methods (Fig. 1*F* and *G*) did not involve occlusion of blood vessels led Corcoran and Page[28, 29] to a study of blood flow through kidneys of animals rendered hypertensive by the Goldblatt technic. If pulse pressure was reduced by partial occlusion of the renal arteries

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and the arterial blood pressure was experimentally increased to permit the normal volume of blood flow, hypertension still occurred. This work suggested that some factor other than ischemia per se was responsible for hypertension.

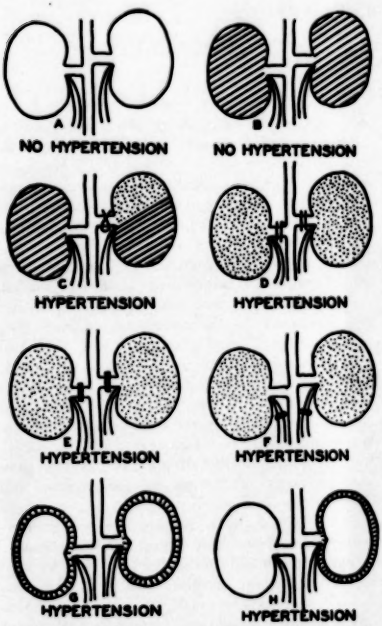

FIGURE 1. *Experimental Hypertension in Animals.*

A — normal kidneys; B — bilateral nephrectomy (usually accompanied by uremia but not by hypertension); C — ligation of renal vessels, with extirpation of nonischemic renal tissue; D — moderate sudden clamping of renal arteries; E — severe sudden clamping of renal arteries; F — obstruction of both ureters; G — cellophane perinephritis.

Hypertension occurs in all these preparations except A and B. In E and F the hypertension is associated with uremia. Preparation H represents a unilateral cellophane kidney. In this, there occurs only a moderate degree of hypertension, which is accentuated if the normal kidney is removed, and disappears if the cellophane kidney is removed. Note that in all instances the injured renal tissue remains in situ. Preparations C and H illustrate the protective influence of normal kidney substance.

Where hypertension resulted from a unilateral cellophane kidney (Fig. 1*H*), Page showed that removal of the sound kidney resulted in increased hypertension, whereas removal of the cellophane kidney resulted in the return of the blood pressure to normal. These observations were also true of a unilateral Goldblatt kidney.[30]

The experimental surgical procedures illustrated in Figure 1 have been interpreted as indicating that a pressor substance is mobilized in ischemic (or otherwise damaged) renal tissue. The fact that this substance can best be demonstrated after removing large amounts of normal kidney has led many investigators to the belief that normal kidney tissue elaborates a substance that inhibits this pressor reaction.*

Renal Extracts

Because of the existence of many pressor substances of nonspecific nature and the absence of any experimental evidence of their clinical importance, Tigerstedt and Bergman's isolation of renin attracted little attention until Goldblatt's[1] work, confirming Cash's earlier observations,[24] became widely publicized.

In 1938, Merrill, Williams and Harrison[31] reported studies in which they established certain differences between Tigerstedt and Bergman's renin and nonspecific vasopressor substances. Page[32] also studied the physiologic action of renin. He found that when it was administered to an animal over a period of time its pressor action tended to disappear, an exhaustion phenomenon that he termed "tachyphylaxis."

In 1939, Page and Helmer[33] found that renin produced no vasoconstriction when perfused with Ringer's solution through a rabbit's ear, but that vasoconstriction did occur if a proteinlike substance, called "renin-activator," derived from red blood cells or plasma, was added. Subsequently, they found that renin and renin-activator could be incubated together to yield a third substance that would produce a sharp adrenalinelike effect. To this substance they gave the name "angiotonin." They described it as a fluorescent substance whose degree of fluorescence was proportional to its pressor activity. They stated that it was heat-stable in acid solutions, and that crystalline oxalates and picrates had been formed from it. Following the work of Muñoz, Braun-Menendez, Fasciolo and Leloir,[34] Page and Helmer[33] suggested that renin was an enzyme, that renin-activator was a substrate, and that the end product of their reaction was angiotonin (Fig. 2).

There is evidence that in addition to pressor substances, certain inhibitors also exist. Freeman[35] showed that if blood was transfused from normal

*An alternative explanation for the protective influence of normal renal tissue is that it excretes the pressor substance. This view is apparently held by most members of the South American group.

dogs to dogs rendered hypertensive by the Goldblatt technic, a fall in blood pressure lasting from six to thirty-one minutes would occur. This sustained fall did not occur when hypertensive dogs were transfused with hypertensive dogs' blood or when normal dogs were transfused with normal dogs' blood.

Page and Helmer[36] considered that tachyphylaxis, or the diminishing effect of renin administered intravenously, was explained by two mechanisms — first, the exhaustion of the supply of renin activator and, second, the presence of so-called "renin-inhibitor." Tachyphylaxis was found to occur to a lesser extent with angiotonin, and angiotonin-activator was found to be present in an acetone-soluble fraction of blood. These workers therefore concluded that angiotonin was probably an intermediary substance and not the final pressor agent. They were unable to differentiate the inhibitory substances in their actions on renin and angiotonin, respectively (Fig. 2). It is generally believed that renin is a substance abnormally liberated as the result of renal injury and that renin-activator and angiotonin-activator are normal constituents of blood.

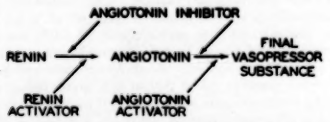

FIGURE 2. *The North American Concept of the Vasopressor Mechanism.*

Renin is a substance mobilized by injured renal tissue. It reacts with renin activator (a normal constituent of plasma) to produce angiotonin, which has a sharp, adrenalin-like effect. Page has produced evidence that the angiotonin then reacts with another constituent of plasma, angiotonin activator, to yield a final vasopressor substance. Inhibitors are not clearly differentiated into those that act on renin and on angiotonin respectively.

South American workers, using different terminology, substantiate the formation of a stable vasopressor substance (presumably angiotonin) from renin and a constituent of plasma. Their evidence suggests that it is the final vasopressor substance. The South American group has found an enzyme that breaks down their substance, but no specific inhibitors.

Work similar to that of Page and his coworkers was carried out independently in Buenos Aires. Muñoz, Braun-Menendez, Fasciolo and Leloir[34, 37, 38] showed that renin had the properties of an enzyme and that the blood globulin factor was a substrate. By incubation in vitro they found that these two substances formed a third substance with the same physiologic characteristics as a vaoconstrictor substance isolated from the venous blood of ischemic kidneys. This third substance, probably identical with angiotonin, they called "hypertensin." The South American group also found that the enzymatic formation of hypertensin was limited by another enzyme that they called "hypertensinase." This substance was found to be present in extracts of many body tissues, especially plasma, liver and spleen.

Hypertensin was shown by these workers, and also by Dexter,[39, 40] to produce no tachyphylaxis when injected into intact animals — although it did so in the isolated rabbit's ear. It is probable, therefore, that the hypothesis of an angiotonin-activator and a final vasopressor substance may eventually be discarded.

Inhibitory Substances

Regarding the nature of possible inhibitory substances there is a wide divergence of opinion. Page[41] found that bilateral nephrectomy increased the pressor response to renin and angiotonin and greatly increased the amounts of these substances needed to produce tachyphylaxis. He concluded, therefore, that in nephrectomized animals the inhibitory substances are not present, and conversely that inhibitors are present in the kidneys of normal animals. Harrison[42] also found that certain pressor substances were more effective in nephrectomized than in normal animals, and concluded that inhibitors exist in normal kidney tissue. The presence of such inhibitors was also suggested by the rise in blood pressure that followed the removal of the normal mate to an ischemic kidney. Conclusions based on increased vasoconstriction in uremic animals must be recognized as open to doubt because of the great vascular sensitivity of such preparations and the confused biochemical balance produced by the retention of metabolites. There is evidence, however, that certain substances capable of neutralizing the action of renin or angiotonin in animals do exist. This problem is now being attacked on the basis of three different concepts, as follows:

(1) The members of the Buenos Aires group are unconvinced of the existence of any specific inhibitor of renal origin. They have produced evidence for the existence of an enzyme, widely disseminated through body tissues, which is capable of destroying the circulating vasopressor substance (hypertensin). Recently Schroeder, Stock and Dobriner,[43] in this country, have demonstrated the effectiveness of aminoxidase isolated from liver tissue in inhibiting the action of a vasopressor substance (presumably angiotonin) in rats. It is probable that hypertensin and an-

giotonin are identical. It is possible that aminoxidase, or some related substance, is the hypertensinase of the South American workers.

(2) Wakerlin and Johnson[44] have demonstrated in dogs the formation of an antibody to pig's renin. They injected this substance into hypertensive Goldblatt dogs and obtained a definite fall in blood pressure, whereas the substance has been found not to lower the blood pressure of normal animals. It is unfortunate that the titer of antibody has in some cases been shown not to parallel the blood-pressure response.[40]

(3) Other American workers have been engaged in the study of specific inhibitors of renal origin. Page and his associates[45] isolated a substance with which they treated a large number of patients. Although definite reduction in blood pressure usually resulted, the greatest effect was noticed when a febrile or local tissue reaction occurred. The possibility of a nonspecific foreign-protein effect cannot be entirely dismissed. Grollman, Williams and Harrison[46-48] have also been working in this field and have demonstrated the blood-pressure-lowering effect of extracts of renal substance on hypertension in rats, dogs and human beings. They have recently further fractionated their extract[49] so as to eliminate the nonspecific action of concentrated salt, an error to which their earlier experiments were possibly subject. Although the new extract has been used only in rats, it appears to be specific in its effect. It requires 200 to 300 gm. of kidney to prepare one day's dose for a rat.

Renal Hypertension in Man

Although the renin mechanism in animals has been firmly established, direct evidence of its existence in man depends on perfusion experiments through isolated organs, a technic that is open to many nonspecific results. Many of the clinical reports of cases of human hypertension cured by nephrectomy are not entirely convincing. The following case history is unique in that the patient was followed for two years with normal blood pressure before the development of his illness and for one full year after nephrectomy.

Case Report

A 39-year-old, married automobile service agent was first seen by one of us (R. E. D.) on September 17, 1938, because of recurrent episodes of low-back pain and vague abdominal discomfort, characterized chiefly by distention, pain in the right lower quadrant of the abdomen and constipation over a period of 6 years. The past history was irrelevant except for rather frequent prolonged sore throats. There were occasional frontal headaches, but no dizziness, throbbing or tinnitus, and no symptoms referable to the urinary tract. The height was 66 inches, the weight 171 pounds, the pulse 88, the temperature 99°F., the hemoglobin 88 per cent (Dare), and the blood pressure 128/82.

Physical examination revealed a well-developed and moderately obese, healthy-appearing male. Examination of the eyes and ears was normal. The nasal septum was deviated slightly to the left. The tonsils were red, swollen and ragged, and yielded purulent material on pressure. There was no submental, cervical, axillary or inguinal adenopathy. The heart was normal in size, with regular rhythm and no murmurs or thrills. The lungs were clear throughout, the abdomen soft to palpation, and the genitalia normal. The extremities and tendon reflexes were normal. A specimen of urine was clear, concentrated to a specific gravity of 1.024, was acid in reaction (pH 4.5) and contained no albumin or sugar; the sediment was normal. Blood Wassermann and Kahn tests were negative. The patient was given advice concerning the proper care of his intestinal tract and was told to have his tonsils removed when the infection in them had subsided.

In August, 1939, the chronically infected tonsils were removed. Six days after the operation, consolidative inflammatory changes developed in both lung fields, and the patient was hospitalized for 1 month. During the following year the patient was seen on several occasions for minor complaints, at which times the blood pressure was routinely recorded (Fig. 3).

On December 7, 1940, after an interval of 6 months during which he had not been seen, the patient again reported because of almost constant, pounding headaches and dizziness. There was also an intensification of the backache noted at the first interview. The physical examination was similar to that already recorded except that the tonsils were absent and the blood pressure was 170/100. The urine showed a specific gravity of 1.020, was acid (pH 5.5) and contained no albumin or sugar; the presence of an occasional red cell was suspected. Because of the patient's urgent request for relief of symptoms, he was given potassium thiocyanate (300 mg. daily) and phenobarbital (8 mg. four times daily). This brought marked symptomatic relief and was therefore continued throughout the ensuing period of observation and investigation, though it probably affected subsequent blood-pressure readings.

During the following month investigation was undertaken while the patient was ambulatory. A complete examination of the back by an orthopedist showed no abnormalities, but the following day the patient reported lameness in the right kidney region as a result. A neurosurgeon was also consulted, who observed slight but definite changes in the caliber of the retinal vessels, but found the neurologic examination entirely normal. Roentgenographic examinations of the back and the skull were normal. Urine examination was negative except for the presence of a faint trace of albumin. A phenolsulfonephthalein test of renal function showed 25 per cent dye excretion in 15 minutes and 55 per cent in 1 hour. An intravenous pyelogram showed normal excretion from the left kidney but none from the right. Cystoscopy was therefore performed by one of us (C. M.). Retrograde pyelograms revealed a large right hydronephrosis with apparent constriction of the right ureter near the ureteropelvic junction (Fig. 4). Multiple stone shadows were visible at the lower pole of this kidney. Urine from both ureters was sterile, and contained 0 to 5 red cells, 0 to 3

white cells and occasional epithelial cells, but no casts, per high-power field.

On January 14, 1941, a right nephrectomy was performed by one of us (C. M.) through an oblique right-loin incision. There were many fresh granulations around the capsule of the kidney, which bled when they were severed. When the region of the pedicle was dissected a very large extrarenal hydronephrotic pelvis was seen. As this interfered with visualization of the renal pedicle, a gall-bladder trocar was inserted through the kidney cortex and the pelvis was decompressed. There was a marked U-shaped angulation of the ureter near the pelvic junction. This was bound down with many firm adhesions. These were freed, and the organ was removed.

The pathologic specimen measured 12 by 7 by 4 cm. The pelvis and calyxes showed a marked degree of dilatation. The mucosa of the pelvis was congested in a purpuric manner. Several calculi averaging 3 mm. in diameter were present in the lower calyxes. The pelvis was largely extrarenal and was attached to a portion of ureter 2 cm. in length, which was of normal caliber. Microscopically there was a definite diffuse chronic inflammatory reaction throughout the cortex. There was moderate dilatation of the glomerular spaces. The tubules were well preserved. The pelvic epithelium was thin and beneath it there was evidence of extravasation of old and recent blood.

The postoperative hospital course was satisfactory, and during this time the blood pressure gradually fell. The patient was discharged on the 16th hospital day completely relieved of his head discomfort. For several weeks he was comfortable at rest but experienced a recurrence of his pounding headache when he returned to work. During this time his resting blood pressure was normal, but he showed an abnormal rise on slight exertion. This eventually subsided, and he has now been back at his work for 8 months without any return of symptoms.

Discussion

The occurrence of occasional cases of renal hypertension due to unilateral kidney involvement is established beyond reasonable doubt. The failure of several statistical studies to unearth such cases attests their rarity but not their nonexistence.

If the experimental procedures summarized in Figure 1 are transferable to human physiology, there are several possible reasons why these cases should be uncommon. It is apparent that considerable renal tissue must be damaged to produce enough renin (or similar substance) to effect a significant change in blood pressure. When one considers that this substance may be neutralized by the protective influence of the normal kidney in addition to the normal portions of the diseased kidney, as well as by possible enzymes or antibodies, the absence of hypertension in many cases of unilateral renal disease can be understood. It is entirely possible that there are individual variations in the amounts of renin formed and in the protective effect of normal tissue present. If this

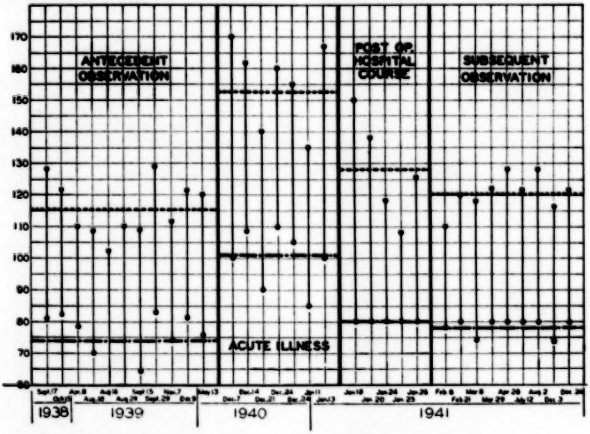

Figure 3. *Blood-Pressure Chart of Patient with Renal Hypertension.*

The ordinate represents millimeters of mercury. Dates of individual determinations are recorded along the abscissa. The dotted lines represent mean systolic pressures, and the broken lines represent mean diastolic pressures for the periods indicated. The extremely low readings during the period of antecedent observation occurred during the course of a postoperative inhalation pneumonitis.

supposition is correct, it is those persons with defective protective effect or with an exaggerated tendency to liberate renin who are most likely to develop hypertension from unilateral renal disease. A second factor that may be important in this connection is age. Many of the most dramatic cases reported in the literature were found in children. Another factor may be the type of renal lesion. The reported cases have occurred in association with various types of renal lesions, notably pyelonephritis, hydronephrosis, tuberculosis and tumor. If the work of Corcoran and Page[28, 29] is confirmed, it is probable that the important type of lesion is not necessarily a vascular one that produces ischemia, but rather any type of lesion that interferes with pulsation in the renal vessels or tissue. Such lesions include vascular obstruction, ureteral obstruction with increased tissue tension, constricting perinephritis and certain exudative reactions.

Several bizarre lesions have been described in the literature. Howard, Forbes and Lipscomb[9] have reported a case of aneurysm of the left renal artery in a child of five. This patient had extensive sympathectomy and decapsulation of both kidneys without relief of his hypertension, but when the left kidney was removed, the blood pressure promptly dropped to normal. An aneurysm might be expected to reduce pulse pressure in the kidney. Another bizarre case is that of Leadbetter,[10] in a five-year-old child with an ectopic kidney, the artery of which was partially occluded by a mass of

FIGURE 4. *Retrograde Pyelogram of Patient with Renal Hypertension.*

Note the large hydronephrotic pelvis of the right kidney. The ureter was practically obstructed. There was no filling of the right pelvis by intravenous pyelography. The kidney showed a diffuse inflammatory reaction throughout the cortical area and a proliferative perinephritis.

smooth muscle. After removal of the kidney the blood pressure returned to normal. This case is a human example of the principle involved in the application of Goldblatt's clamp. The case reported by us had almost complete obstruction of the right ureter. The combination of obstruction and limitation of elasticity in the capsule may well have contributed to limited vascular pulsations in this case.

The uncommon occurrence of cases of hypertension due to unilateral renal disease does not necessarily indicate that the mechanisms outlined occur with equal rarity. If there are proved unilateral cases, presumably there are bilateral cases that cannot be proved by nephrectomy. In view of the fact that there is less normal renal tissue to exert its protective effect, such cases may outnumber the unilateral ones.

It would be premature to draw conclusions about the etiology of essential hypertension. It is probable that the number of human cases of renal hypertension is larger than the sporadic reports of proved unilateral disease indicate.

Summary

The experimental basis of renal hypertension is discussed. The renin mechanism in animals appears to be definitely established. There are isolated instances of renal hypertension in man. These cases may be due to the renin mechanism.

A case of unilateral renal disease with hypertension is reported. The blood pressure was followed for two years before the onset of hypertension and for one year after recovery, which was instituted by removal of the diseased organ. The specimen was unusual in that there was an extensive granulating perinephritis in addition to an almost completely occluded ureter.

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MEDICAL PROGRESS

THE MECHANISM OF HEART FAILURE AND RELATED STATES*

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ALTHOUGH heart disease and heart failure are among the commonest and most serious conditions that afflict mankind, the average doctor is inclined to accept empirically the symptoms and signs that occur, and makes little attempt to relate them to the actual physiologic disturbances of the circulation. This attitude is taken in spite of the fact that the heart and blood vessels constitute a physical system in which vital biologic processes are less important than in the functioning of many other organs. In recent years an impressive accumulation of experimental evidence has added to knowledge in this field, and has permitted cardiologists to buttress some of their theories and to discard others.

The lag in general understanding of the mechanism of circulatory failure is due in part to the highly specialized nature of many of the experimental methods employed; in part to the complicated theoretical considerations involved; and in large part, too, to the fact that many physicians, and even cardiologists, have in the past considered the heart to be an isolated organ and have not paid proper attention to the fact that the heart and the peripheral blood vessels are integral parts of the same system, and that manifestations of heart failure are to a large extent demonstrable only in the peripheral circulation. There is now enough clinical and experimental evidence so that all physicians should have at least a working knowledge of the dynamics of the circulation in heart disease and of the nature of circulatory failure; if they so relate the clinical findings exhibited by their patients they will be better doctors, for their interpretations of signs and symptoms will rest on a sound basis.

So much has been published in this field of medicine in the last few years that it is undesirable to cite a comprehensive series of references. Specific articles will be referred to only when they have appeared recently, and no attempt will be made to cover the field completely. Papers are cited which will add to the understanding of the general practitioner concerning certain manifestations of heart disease and failure.

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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Mechanism of Congestive Heart Failure

Two outstanding theories have been advanced to explain the physiologic mechanism of congestive heart failure. One, the "forward-failure theory," holds that the manifestations of cardiac decompensation are caused in the main by an inadequate output of blood by the heart. This was the belief of Sir James Mackenzie and Sir Thomas Lewis, and represents the point of view maintained until recently by most English and American clinicians. The second, the "backward-failure theory" of heart failure, was first clearly expressed a hundred years ago by James Hope. In the simplest terms it attributes the phenomena of congestive failure to congestion in the vascular circuit behind the failing ventricle. This theory has been accepted by most French and German clinicians ever since Hope's day, and in the last few years has been increasingly adopted by American investigators.

The forward-failure theory is attractive because of its apparent simplicity. The heart being a pump, it might appear at first glance that heart failure consists merely of a failure of this pump to eject sufficient blood. It is now possible to test this explanation experimentally, since in recent years technics have been perfected that are accurate in estimating the cardiac output under various conditions, and many data are now available. No attempt will be made to describe or evaluate these methods, all of which have their limitations, but the results obtained through them are now sufficiently numerous and in close enough agreement to justify certain conclusions.

As regards the relation between cardiac output and heart failure, Harrison[1] concludes, "Persons with congestive heart failure may and often do have diminished circulatory minute volume, but this is not the essential cause of their symptoms." Others have taken issue with this statement. Altschule[2] believes that the fundamental defect in congestive failure is a cardiac output that is low in relation to the metabolic needs of the body and the venous pressure. With this viewpoint Stewart[3] agrees. Subsequent to the publication of these monographs, McGuire and his co-workers[4] dem-

onstrated low cardiac outputs in 3 patients in heart failure with an increase during recovery, but in a fourth patient the more severe the failure, the higher was the output. In another study they[5] found low volume flows in 19 of 20 decompensated patients. The same authors[6] also presented evidence that patients with congestive failure are unable to increase their cardiac output in response to exercise to an extent that is attained by normal persons. Espersen[7] has reported finding normal cardiac outputs in 12 of 27 patients in heart failure, although Seymour et al.[8] obtained low outputs during failure in all the 6 patients studied, and the outputs increased with clinical improvement. Starr,[9] employing an entirely different technic, that of the ballistocardiograph, has presented results indicating that heart failure may occur with normal or even supernormal circulation. The validity of this method has not yet been fully demonstrated, but the results are certainly suggestive. It is also well known that heart failure may occur in conditions characterized by increased circulation (hyperthyroidism, arteriovenous aneurism, anemia and possibly beriberi). It would seem wisest, therefore, in the light of our present knowledge to echo what Starr says:

> The majority of cases [of congestive failure] have subnormal circulations, and improvement in the circulation often coincides with clinical improvement. On the other hand, the relationship is not invariable, and any idea that the symptoms are the direct mechanical consequence of a diminished circulation must be abandoned.

In summary, therefore, our present knowledge suggests that the relation of cardiac output to heart disease and failure is as follows:

In compensated organic heart disease the resting cardiac output is often somewhat reduced, but may be normal or even increased.

In congestive heart failure there is usually a further decrease in cardiac output. The output per beat is especially apt to be impaired. When the output is considered in relation to the oxygen consumption of the body (basal metabolic rate) or to the venous pressure of blood reaching the heart, its diminution is even more evident. Nevertheless, the output is occasionally normal or even increased, either in absolute terms or relatively to the output before failure occurred. The degree of clinical failure does not bear any quantitative relation to the change in output.

With recovery from failure the output usually improves, but rarely to the point that existed before failure.

In the presence of heart disease, exercise increases the cardiac output less than normally; and if congestive failure is present, the increase in flow is even smaller.

The cardiac output may be reduced in many conditions — acute or chronic — in which none of the signs of clinical heart failure are present.

A simple decrease in cardiac output is an inadequate explanation of congestive heart failure.

If, then, the clinical picture of congestive failure cannot be adequately explained by decreased cardiac output alone, what is the causative mechanism? The answer is to be found, not in the outflow of blood from the heart, but in the inflow into the auricles and ventricles. Twenty to thirty years ago, Starling and his associates[10, 11] carried out a brilliant series of investigations on cardiac physiology, and found that an increase in stretching — that is, dilatation — of the muscle, is, accompanied by an increase in the strength of contraction; that the venous pressure is the important factor in controlling this diastolic stretching and hence the cardiac output; and that the rate of metabolic processes of the heart muscle is determined by the length of the fibers rather than by the work accomplished (that is, a dilated heart consumes relatively more oxygen than a normal one).

According to the backward-failure theory of congestive failure, the diseased heart is inefficient, requires a greater venous pressure and hence more dilatation in order to effect a given output of blood, and uses up more energy — that is, consumes more oxygen — in doing so. This results in more and more cardiac dilatation, with an increasing amount of residual blood left in the ventricles in diastole. The presence of this residual blood produces effects transmitted back to the auricles and to the great veins so that blood under increased pressure piles up in the vascular circuit, — either pulmonary or systemic, — and this congestion initiates the train of circumstances that produces the characteristic symptoms of heart failure — dyspnea, edema and so forth. Since in the vast majority of clinical types of heart disease the left ventricle is subjected to greater strain than is the right, it usually fails first, and it is the pulmonary circuit that is engorged. Eventually the strain that this vascular congestion and hypertension impose on the ventricle that has not failed proves too great, and this ventricle in turn fails.

In the controversy that has existed between the backward-failure and forward-failure exponents, one point is not infrequently overlooked which to some extent reconciles the two viewpoints. This is that blood normally must be simultaneously pumped by both ventricles in exactly equal amounts. If one ventricle ejects less than the other, even by a minute amount or for a few beats, blood

tends to pile up in the vascular circuit behind the impaired ventricle, until the venous pressure is sufficiently raised to act as a stimulus for an improved ventricular discharge. Such small and relative changes in volume flow from the two sides of the heart cannot be measured in human beings by any available method, but it is probable that they play a significant role in the pathogenesis of congestive failure, and possibly in the exertional dyspnea of persons with limited cardiac reserve.

Further consideration concerning how back pressure and congestion behind a failing ventricle can lead to clinical manifestations, together with the many secondary factors that contribute to the aggravation of the symptoms, will now be discussed.

Dyspnea

Dyspnea is the cardinal symptom of left ventricular failure and is explainable by the sequence of vascular events described above occurring in the pulmonary circuit. With dilatation of the left ventricle and increase in pressure in the pulmonary veins, there ensues an increased pressure transmitted back into the pulmonary capillaries, with resultant engorgement of these vessels and ultimate exudation of fluid into the alveolar spaces. Consequent on these changes the lungs are stiffened by the dilated, engorged vessels, the vital capacity is diminished, and the residual air is increased. It is known that the respiratory reflex that alternately initiates inspiration and expiration (Hering-Breuer reflex) is dependent on the degree of stretching or stiffening of the lung, and that in experimental animals in which sudden pulmonary vascular engorgement is produced rapid, shallow breathing results.[12] The distressful, rapid, shallow breathing that occurs in clinical heart failure is therefore due in large part to this reflex effect occasioned by the pulmonary congestion. Other factors may play a role, but probably not an important one, except in advanced heart failure or during exercise. Such factors are arterial anoxemia caused by impairment in the pulmonary exchange of gases, and central effects on the respiratory center as a result of failure of an adequate circulation in providing oxygen or removing carbon dioxide or other acid metabolic products.

The cause of paroxysmal cardiac dyspnea is not fully established, but no better explanation has been given than that of Weiss and Robb.[13] In brief, according to their theory the cause is acute left-sided failure, precipitated by one or more trigger mechanisms, all concerned with the inadequacy of the horizontal as compared with the elevated position of the thorax. These advantages of the elevated thoracic position are mechanical factors aiding breathing, decrease in the hydrostatic element of both peripheral and pulmonary venous pressure, and a slight and possibly inconstant decrease in cardiac output. In addition, when a cardiac patient assumes the recumbent position after having been up and around during the day, there may be a well-marked increase in plasma volume due to the mobilization of extravascular fluid. This added circulatory burden was suggested by Weiss and Robb, but it remained for Perera and Berliner[14] to demonstrate it unequivocally in cardiac patients subject to paroxysmal dyspnea.

A possible role of neurogenic reflexes in the precipitation of these attacks was also brought out by Weiss and Robb. However, that such a role is contributory only is the belief of the majority of investigators.

Edema and Diuresis

Until comparatively recently the explanation of edema of cardiac origin seemed to be simple. Since there is an increased pressure in the peripheral veins in right-sided heart failure, it was logical to assume that this heightened pressure is conveyed back to the capillaries, thus increasing the hydrostatic pressure and the tendency for more fluid to be driven into the tissue spaces. Fahr and Ershler[15] have shown that edema is likely to form when the hydrostatic pressure at the venous end of the capillary loop rises to within 2 mm. (mercury) of the colloid-osmotic pressure of the plasma. However, the complexity of the factors contributing to edema formation is becoming increasingly evident, as Altschule[2] has brought out, and he has shown that the degree of edema does not bear any absolute relation to the height of the venous pressure. Several elements enter into the control of the level of pressure in the venous system. Not only is the ability of the heart to pump forward the blood reaching it important, but peripheral conditions modify the pressure level. The degree of constriction of the blood vessels in various parts of the vascular circuit is one prominent factor. A lowered venous tone tends to lower the venous pressure; increased arterial tone with a normal venous tone tends to shunt blood into the venous channels, and hence to increase the venous pressure. The total volume of circulating blood also plays a vital role, as has been brought out by Bazett.[16]

It has been shown[8, 17, 18] that the blood volume is often increased in heart failure, especially that of the chronic right-sided type. The assumption has frequently been made that this increase in plasma volume is the result of the train of circumstances consequent on a high venous pressure and an increase in the peripheral vascular bed, and that with improvement and the onset of diuresis this

train of events is reversed; that is, the venous pressure falls owing to improved cardiac action, the plasma volume decreases because of better renal activity as the result of improved renal blood flow or the effect of diuretics, and fluid returns to the blood stream from the tissues and is excreted. However, a number of recent observations do not conform to this simple explanation. Stewart[19] found evidence that the plasma proteins fall with the onset of diuresis, suggesting that fluid enters the blood stream to dilute the plasma *before* diuresis commences. Swigert and Fitz[20] also found the plasma volume sometimes increased after giving a mercurial diuretic, as though the fluid were first mobilized from the tissue, before renal excretion took place. Calvin, Decherd and Herrmann,[21] however, found such an increase in only 2 cases following the administration of Salyrgan, and in these patients diuresis was delayed or failed to occur. In 13 other cases where prompt diuresis took place the plasma volume diminished. Of significance, too, is the observation of Futcher and Schroeder[22] that some patients with cardiac edema apparently have a specific tendency to retain sodium and that their loss of edema fluid follows a change in the sodium balance. Warren and Stead[23] are of the belief that edema develops in congestive failure because the renal excretion of salt and water is altered by a decreased cardiac output, and that this increase in extracellular-fluid volume is accompanied by an increase in plasma volume that eventually causes a rise in venous pressure. Support for the thesis that a rise in venous pressure *follows* an increase in plasma volume is to be had in the work of Starr,[24] who showed that the pressure in the veins and other parts of the vascular circuit after death of patients dying in congestive heart failure is markedly higher than in those dying of other causes. He interpreted this as possibly due to an increased blood volume that overloads the vascular system.

It has not yet been conclusively shown in what way the venous pressure, as measured in the usual fashion in the antecubital vein, reflects the pressure in the capillaries on the one hand and in the right auricle on the other. There is evidence that normally the antecubital venous pressure is higher than that in the right auricle by several centimeters of water,[25] but this gradient is abolished in patients and experimental animals with right-sided heart failure and elevated venous pressure.

The explanation for these various observations, at variance with the usual concept of edema formation and diuresis, is not entirely clear, but it has been suggested by Schroeder and by Warren and Stead that hormonal influences may be involved in the retention of electrolytes. It is well known that the hormones of many of the endocrines exert some antidiuretic effect[26] and that actual heart failure in patients with Addison's disease may be precipitated by an overdosage of desoxycorticosterone,[27–30] owing to excessive sodium retention and increase in plasma volume.

Thus the exact relations and the causal connections between the level of venous pressure and the degree of heart failure remain unsolved problems. It is not unlikely that a vicious circle is established whereby right-sided heart failure produces vascular congestion and a tendency toward increase in pressure in the systemic venous reservoir. This in turn initiates a sequence of events that may maintain or further elevate the pressure regardless of the cardiac status itself. These other factors affecting edema formation deserve consideration.

Landis and Gibbon[31] and Sodeman and Burch[32] have pointed out the importance of tissue pressure in controlling edema formation. Persons with firm, elastic subcutaneous tissues accumulate edema much less readily than do those whose tissues have lost their elasticity and are readily stretched, such as old people and those who have lost weight or who have previously been edematous.

The role of a lowered plasma osmotic pressure in cardiac edema has also come in for a good deal of study, and it is now well known that the plasma proteins and especially the albumin fraction may be significantly lowered. Several factors may contribute to this lowering: impaired intake of protein; deficient absorption; increased loss through the kidneys, into serous effusion or into edema fluid itself; defective formation due to hepatic congestion; and hydremia or increase in plasma volume without a concomitant increase in plasma protein. The lower the plasma osmotic pressure from whatever cause, the less the increase in hydrostatic pressure that is required to initiate edema formation.

Another factor that may play a part in edema formation is capillary anoxemia, which causes dilatation and increased permeability of the capillaries. Smirk's[33] experiments indicate that such anoxemia is important in the production of cardiac edema, but Fahr and Ershler[15] are of the opinion that it plays little or no part. The fact that the protein content of cardiac edema fluid is low, averaging less than 0.5 per cent, indicates that increase in capillary permeability does not progress to a point permitting the passage of protein in high concentration.

Deficient lymphatic drainage from the tissues has been said to occur in patients with edema of

cardiac origin,[34] and this factor too may play some role in edema formation.

In summary, the mechanism of edema formation is dependent on the interrelation of a number of factors, which may be disturbed singly or in combination. However, the bulk of experimental evidence still favors the belief that the underlying condition that initiates the train of events producing edema in congestive heart failure is failure of the right ventricle. This leads to peripheral venous engorgement and a tendency toward a rise in systemic venous pressure, with enlargement of the vascular bed, an increase in blood volume and a rise in capillary hydrostatic pressure.

When this primary cardiac factor tending toward the production of edema has become operative, the secondary factors come into play, and under certain conditions — especially in chronic congestive failure — they may become of major importance, outweighing the initial cause. These secondary factors are as follows: a possible capillary anoxemia, with dilatation and increased permeability due to a reduced systemic blood flow; a decrease in plasma osmotic pressure; a decrease in tissue pressure; a possible defective lymphatic drainage; and a change in electrolyte balance due to dietary factors, to depression of renal activity or possibly to hormonal influences. The fluid retention in heart failure is found not only in the tissues as edema but in the blood as increased blood volume, and it should be remembered that many of the factors that lead to the development and the relief of peripheral edema are also operative in the lungs when pulmonary congestion occurs as the result of left-sided failure.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 29091

PRESENTATION OF CASE

A twelve-year-old boy was referred to this hospital with a diagnosis of pneumonia.

Three days prior to admission the patient complained of epigastric pain and on the next day ate poorly and did not seem well. However, there were no other signs or symptoms. On the day prior to admission he vomited ingested food and his temperature was elevated to 103°F. His physician found signs of consolidation in the right lung, and because of fever, 2 gm. of a sulfonamide drug was administered. On the day of admission he developed a hacking nonproductive cough. At no time had he experienced chills.

The family history was noncontributory. For three and a half years the boy suffered with repeated attacks of otitis media and mastoiditis necessitating bilateral drainage of the middle ear and resection of the mastoid cells on the left side. Three years before entry, because of a suspected brain abscess, an exploration was made through the right temporal bone; no abscess was found. Six months previously, because of recurrent pain in the left mastoid area and profuse drainage of pus from the ear, mastoid resection was revised. He was treated with a course of orally administered sulfadiazine totaling 46 gm. in nineteen days. *Staphylococcus aureus* and a beta-hemolytic streptococcus were cultured from the pus.

Physical examination revealed an acutely ill, cyanotic, obese boy. Respirations were rapid and shallow, and there was an occasional hacking nonproductive cough. The mucous membranes were congested and dry. The heart was normal. The right chest was dull from the midscapula to the base. Bronchial breathing and bronchophony were prominent throughout the right chest posteriorly in the axilla and to a less marked degree anteriorly at the base. The abdomen was soft, and no masses were felt.

The blood pressure was 110 systolic, 70 diastolic. The temperature was 105°F., the pulse 90, and the respirations 60.

The white-cell count was 26,000. The urine was acid, had a specific gravity of 1.015 and gave a ++++ test for albumin; the sediment contained an occasional white cell, an occasional red cell and many hyaline and granular casts.

A chest roentgenogram taken in the horizontal position showed increased density throughout the greater portion of the right lung field more marked in the medial two thirds of the lung. The density had a ground-glass appearance and was more marked at the base. The heart was slightly displaced to the left. The left lung was not remarkable. No pathogens were grown from the sputum, and only obvious contaminants were found in the blood culture.

Despite the intravenous administration of 10 gm. of sodium sulfadiazine during the first day, producing a blood level of 15.6 mg. per 100 cc., the boy became increasingly restless and disoriented. The pulse rose above 120, and he died approximately thirty hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: In the first place, I am sort of hipped on blood smears, and I should like to comment that with a white-cell count of 26,000 in a boy with a temperature of 105°F., and findings in the chest, a good deal of stress might justifiably be laid on the type of blood picture. The white-cell count was done in the Emergency Ward, and no differential count is given anywhere in the record. I should suspect it showed 94 per cent polymorphonuclears, 6 per cent lymphocytes, no eosinophils and no monocytes. On the other hand, because nothing is said about the differential count, perhaps we can accept it as normal — that is of great significance. I doubt if it was. I should also guess that the boy had a red-cell count of 3,500,000 with a hemoglobin of 11.6 gm.

The questions I should ask in regard to this boy are: Did the previous sepsis have anything to do with the present illness? Did the boy have pneumonia? Did he have empyema? And finally, did he have amyloid disease or did he have nephritis of some type? These are the questions I have to answer, but I am not sure that I am going to be successful.

In the first place, did the previous sepsis have anything to do with the immediate illness? My inclination is to suspect a pneumonic process which had nothing to do with the previous mastoid infections. In other words, I think he did have pneumonia on the evidence here submitted. I suspect the presence of pneumonia from the history of the onset and from the physical findings. The question is, Were the physical findings

definitely those of consolidation or could they have been those of fluid and compression of the lung?

Whether he had empyema or not, I am not sure. If it was empyema, one would be surprised to find such definite evidence of it so soon in the course of the recent illness. One would have to believe he had had it for some time.

Finally, in regard to his kidneys, there was a moderate reduction in the specific gravity. There was a large amount of albumin, which is greater than I should expect with a temperature of this degree, especially when it was associated with a gravity that was somewhat low. If it were not for the granular casts I should be thinking definitely in terms of some type of nephrosis—especially amyloid disease, because of the previous sepsis. I do not see how I can rule amyloid disease out or in on the basis of this history. The questions are whether he had amyloid disease of the kidney, whether he had subacute nephritis or whether the renal damage could be attributed to a reaction from sulfadiazine, which was given six months before entry for a course of nineteen days. I have not heard of any cases of kidney disease that progressed for six months after the cessation of the use of sulfadiazine or any of the sulfa drugs. I should say he had either subacute nephritis or amyloid disease and I shall make final diagnoses of pneumonia, chronic suppurative mastoiditis and kidney disease, possibly amyloid in nature.

I have not looked at the x-ray films. Dr. Mallory intimated to me that Dr. Schatzki was particularly interested in them. I should think I might be allowed to look at the plates first, and Dr. Schatzki can discuss them afterward.

This film was taken with the patient in the horizontal position and the question comes up, Was this one of those cases of so-called "localized edema" of the lungs associated with renal disease in which Dr. Mallory thinks that there is some sort of a consolidating process? Am I wrong in saying that?

Dr. Tracy B. Mallory: I am still uncertain what that lesion really is. In such cases, the lungs usually appear more hemorrhagic than edematous.

Dr. Richardson: I do not know much about x-ray films, and I shall not go out on a limb on that diagnosis in this case. I want to mention it knowing that Dr. Schatzki is going to talk about these films. From this film, I cannot rule out the possibility of fluid in the right chest. The heart seems to be pushed somewhat to the left. I am going to put in a question of empyema in addition.

Dr. Richard Schatzki: This case was presented to the X-ray Department from the Emergency Ward with a clear-cut diagnosis of lobar pneumonia. For several reasons, the dangers in the chest looked somewhat different roentgenologically from those of the common variety of lobar pneumonia. The area involved was rather large but not dense. It had a translucent, ground-glass appearance, as the record states, apparently owing to alveoli that were not yet involved by the process. The medial portions of the lung were much more involved than the peripheral ones. All this made us think that it might well be a localized pulmonary edema. We could not rule out pneumonia, in addition to the pulmonary edema. We certainly thought that the kidneys should be checked. This was done, resulting in the findings that are mentioned.

Dr. William B. Breed: Dr. Richardson, I suggest that the person who abstracted this record perhaps took a little too much on himself in the last paragraph when he said, "Despite the intravenous administration of 10 gm. of sodium sulfadiazine during the first day, producing a blood level of 15.6 mg. per 100 cc., the boy became increasingly restless and disoriented. I suggest that he might have said "because of." That is a high blood level, and the boy had had a large amount of sulfadiazine six months previously. I am not sure that the treatment was not a factor in his rather sudden demise.

Dr. Richardson: Fifteen milligrams does not seem to be an unusual level. It is frequently attained without serious toxic symptoms.

Dr. Allan M. Butler: Was the 10 gm. given intravenously at one time? I think that is a lot.

Dr. Mallory: It was divided into at least two doses.

Dr. Butler: How far apart?

Dr. Mallory: It was spread over twenty-four hours. There is no further comment.

Dr. Butler: Before we hear the diagnosis, I should like to ask Dr. Schatzki if there is prominence of the right border of the heart at the base.

Dr. Schatzki: No; I think it is normal considering the conditions under which the film was taken.

Dr. Fuller Albright: This boy was in the hospital about twenty-four hours. I saw him in an oxygen tent, and he was obviously extremely sick. To me, he obviously had a pneumonia. The localized edema of the lungs that Dr. Schatzki has mentioned would be most unusual. The only question in my mind was whether he had acute cardiac failure. We felt sure it was pneumonia. We did not get a differential count, which was unfortunate. It might have given a clue.

Dr. Butler: There were many hyaline and granular casts in the urine. I do not know whether the boy was dehydrated or not.

DR. ALBRIGHT: The high fever and passive congestion could explain these. One certainly observes casts with high fever.

DR. BUTLER: Yes, but the specific gravity was only 1.015, which means the urine was not concentrated. With high fever, casts and red cells in the urine are usually associated with a concentrated urine.

DR. ALBRIGHT: That is true, but I must confess that I am not disturbed about it.

DR. MALLORY: I shall describe the anatomical findings and then ask Dr. Schatzki to speak again.

CLINICAL DIAGNOSES

Lobar pneumonia.

DR. RICHARDSON'S DIAGNOSES

Chronic suppurative mastoiditis.
Pneumonia.
Kidney disease (? amyloid).
Empyema?

ANATOMICAL DIAGNOSES

Acute glomerulonephritis.
Subacute mastoiditis.
Pulmonary edema.
Pneumonia.
Operative scar: decompression wound.
Focal encephalomalacia, old, inactive.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy this boy had large, distended and heavy lungs. The peripheral portions of the lungs in all lobes were well aerated, whereas the central portions were practically consolidated, with obviously a great deal of fluid in the alveoli. The lungs did not show any granular foci. Our impression in gross was that this was a massive degree of pulmonary edema centralized in the hilar regions and not present in the peripheral portions of the lung. The kidneys were of normal size. When sectioned, the cortices seemed paler than normal and bulged a little bit over the capsule, but in gross we could not be certain of nephritis. The sections, however, show an obvious acute intracapillary glomerulonephritis. The sections of the lungs are much more difficult to interpret. They look frankly pneumonic, with a great many leukocytes and some fibrin, but also a good deal of free fluid and a great many red cells. It is well within the limit of possibility, and as a matter of fact I think it probable, that these lungs were edematous at first and became pneumonic terminally — in other words, that the pneumonia was secondary rather than primary. However, I cannot prove that on histologic grounds.

I think all of us have been impressed with the way Dr. Schatzki looks at a chest plate and often diagnoses nephritis. All of us have seen him do it too often for it to be pure coincidence. I am convinced that there is something in it. The nature of this pulmonary lesion is difficult to explain. It is different from the ordinary types of pulmonary edema that we see in other conditions. Pulmonary edema usually takes one of two forms. In one, there is an obviously wet lung. Frothy fluid bubbles from the bronchi when you press on the lungs, and pours in abundance from cut surfaces of the pulmonary parenchyma. That is what one sees with acute heart failure and with so-called "cardiac asthma." In the other type of pulmonary edema the fluid is not readily expressed by pressure. It seems to be of a gelatinous consistence, and when the lung is fixed it is precipitated as a diffuse colloidlike sheet in the alveoli rather than as granular detritus. In either type small numbers of red cells may be found in the alveoli. The lesions in the group of nephritic cases that Dr. Schatzki has been interested in do not look like those of either type of ordinary edema. The gross appearance of the lung is that of scattered hemorrhages, and microscopic examination always shows more obvious hemorrhage than edema. There is always fluid as well, but the red cells are so numerous that they predominate the picture. There is apt to be some fibrin, and there may or may not be leukocytes. In this case there were so many leukocytes that if I did not have the history, I should have passed it over as ordinary pneumonia.

A PHYSICIAN: A fatal course in twenty-four hours is extremely unusual for pneumonia. Furthermore, a pneumonia involving all five lobes is rare in the absence of a predisposing factor. What does the negative culture mean?

DR. MALLORY: I do not know. I wish we had been more impressed with the idea of pneumonia at the time of death and had cultured the lungs more carefully than we did. Certainly, the negative sputum makes me suspicious that it was not the usual pneumococcal pneumonia.

DR. SCHATZKI: The post-mortem film of the chest is interesting. It looks practically like that of a stillborn baby. There is barely any air in the lungs. The right lung has none, but there is a little in the periphery of the left lung, as you can see. It seems to me that the coincidence of these pulmonary lesions with nephritis, as Dr. Mallory points out, is too common to be laughed off. In some of these cases the films of the chest look exactly like those of cases of pulmonary edema of cardiac origin; the changes are bilateral and fairly symmetrical. In others, the pulmonary le-

sion is asymmetrical and less characteristic. The roentgenologic picture, as well as the clinical course, is not that of pneumonia.

DR. MALLORY: Would you be able to distinguish the picture from so-called "rheumatic pneumonia," Dr. Schatzki?

DR. SCHATZKI: I have not seen many cases of rheumatic pneumonitis. The films in these few cases showed changes that looked roentgenologically like those of localized pulmonary edema, and the patients acted much the same. From talking with you, Dr. Mallory, and with Dr. Bland, I have been impressed that these two conditions are also similar histologically.

DR. MALLORY: I am inclined to think that the histologic picture is the same in certain cases.

DR. FLETCHER H. COLBY: Is there any possibility that the previous sulfadiazine had anything to do with the picture?

DR. MALLORY: This was acute glomerulonephritis, and there was no sign of sulfadiazine involvement. The process was acute and had not reached a stage where the boy would have died of renal insufficiency if he had not had the pulmonary complication.

DR. RICHARDSON: Did he have fluid in the chest?

DR. MALLORY: Only 6 or 7 cc. on each side.

DR. ALBRIGHT: May I ask Dr. Schatzki a few questions? I want to be sure I understand this. In certain cases of kidney disease, is there edema in the lungs that is not due to low serum protein, not due to generalized anasarca, and not due to hypertension and cardiac failure? What is it? Can you be sure it is not caused by pneumonia?

DR. MALLORY: It might be a sterile pneumonia like the sterile pericarditis one sees in uremia. Other well-known inflammatory lesions in uremia are, of course, colitis and gastritis. This may be a pulmonary manifestation of the same type of capillary injury.

DR. ALBRIGHT: In other words this is a pneumonia for which you can find no bacteria. I cannot see why you cannot get acute pneumonitis from the same bug that is causing the trouble in the kidney; that is, the same process is going on in the lung as in the kidney.

DR. MALLORY: For one thing the streptococcus is not found in the kidney, and you do not ordinarily find streptococci in these lungs. However, the problem is difficult to solve with post-mortem studies since edema fluid is an ideal culture medium and so many organisms grow luxuriantly in it that mixed cultures are the rule and are often impossible to interpret.

DR. SCHATZKI: A few facts are difficult to fit in with your theory, Dr. Albright. A number of these patients did not have acute glomerulonephritis, but chronic or subacute glomerulonephritis. In some of them, the pulmonary lesions developed simultaneously with generalized anasarca.

DR. ALBRIGHT: Localized edema of the lung and generalized anasarca?

DR. SCHATZKI: In addition, a number of patients showed no clinical evidence of infection. Furthermore, in several cases at autopsy the histologic picture was not that of pneumonia but that of hemorrhage.

DR. ALBRIGHT: Hemorrhagic exudate?

DR. MALLORY: Yes; it looked as if the capillaries let red cells through instead of merely fluid.

A PHYSICIAN: No white cells?

DR. MALLORY: Only a small number such as you might expect in proportion to the red cells.

DR. JOSEPH AUB: You call this "localized edema." What is the evidence of this edema?

DR. SCHATZKI: It has the roentgenologic appearance of localized edema as seen occasionally in pulmonary edema of cardiac origin. The picture is more obvious in cases with symmetrical bilateral pulmonary edema.

DR. MALLORY: Have you not had some cases with acute nephritis in which the x-ray picture cleared up with dramatic suddenness in twenty-four hours?

DR. SCHATZKI: That is right. It is rather hard to connect that with pneumonic consolidation.

DR. BUTLER: To me there is something odd about this patient, if he had acute glomerulonephritis.

DR. MALLORY: It is a frequent sequel of mastoid disease.

DR. BUTLER: Yes, but these patients do not die of uremia and acute glomerulonephritis in a course of three days.

DR. MALLORY: We are not claiming that he did, Dr. Butler.

DR. BUTLER: All right. Then if his death was due to nephritis, he ought to have had either cardiac failure with hypertension or a crisis of hypertension earlier, in the first few days of the acute process. He had diminished concentration of urine, and it seems to me that the story and findings are not consistent with death and acute hemorrhagic nephritis.

DR. MALLORY: The patient died because he could not breathe, died because of his lung condition.

DR. BUTLER: How often do you find that in the lungs without hypertension or cardiac failure or without uremia?

DR. MALLORY: One can have acute cardiac failure in nephritis without hypertension, according to Longcope.*

DR. BUTLER: Yes, but there is nothing in the physical examination to give evidence of cardiac failure.

DR. ALBRIGHT: We thought clinically that there was a possibility of cardiac failure.

CASE 29092

PRESENTATION OF CASE

A twenty-seven-year-old housewife came to the Out Patient Department of the hospital because of pain in the right lower quadrant of the abdomen.

Approximately five years prior to admission the patient noted the onset of attacks of nonradiating pain in the right lower quadrant of the abdomen. This was usually knifelike but occasionally was crampy and caused her to double up. These attacks usually lasted about an hour and were relieved by bed rest. The pain often occurred every two or three weeks but bore no apparent relation to the menstrual cycle. Simultaneous with the episodes of pain a mild leukorrhea developed, but the patient denied any exposure to venereal infection. Between attacks the patient had a constant dull ache in the right lower abdomen. There were no gastrointestinal symptoms associated with the illness. For the past several months she had had nocturia two or three times every night.

The family history was noncontributory. The patient had had a normal child eleven years previously. At about the same time her first husband died of pneumonia, and she remarried four years later. Although both she and her husband desired a child, no pregnancies had occurred.

Physical examination disclosed slight tenderness in the right lower quadrant of the abdomen, but no mass was felt. There was some thickening of the left broad ligament, and a 4-cm. tender mass was felt in the right vault that seemed connected with the fundus of the uterus. There was a slight erosion of the cervix, with a profuse vaginal discharge. A cervical smear and culture were negative for the gonococcus.

The urine was acid and had a specific gravity of 1.030; the sediment contained an occasional red cell, 7 white cells and 15 epithelial cells per high-power field.

The patient was started on sulfadiazine and warm vaginal douches, and was told to rest in bed. During the next two weeks, the discomfort gradually improved and the vaginal discharge was reduced. The right adnexal mass seemed to persist but was only slightly tender. After two weeks the sulfadiazine was discontinued but the patient was instructed to continue the warm vaginal douches. Several days later she had a sudden attack of crampy pain that caused her to double up. Ice packs applied to the abdomen temporarily relieved the pain but she continued to have a steady dull ache in the lower abdomen. She was then admitted to the ward.

The menarche started at fourteen and the periods were always regular, with a twenty-eight-day cycle, and lasted three days, with no pain. The last catamenia began five days before she entered the hospital.

Physical examination revealed a well-developed young woman in no obvious distress. Examination of the heart and lungs was negative. There was marked tenderness to direct pressure in the right lower quadrant of the abdomen. No rebound tenderness could be elicited, and no masses were felt. On vaginal examination there were definite tenderness and thickening in the right vault. One examiner described a moderately tender right adnexal mass about the size of a small orange. The cervix was lacerated and seemed soft. The uterus was slightly enlarged and was freely movable. A small amount of white discharge was present in the vagina. There was tenderness on the right side of the rectum.

The blood pressure was 124 systolic, 85 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 20.

The examination of the blood revealed a hemoglobin of 95 per cent and a white-cell count of 10,000. The urine was negative. A blood Hinton test was negative.

An operation was performed on the fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRED SIMMONS: Many of the data presented in the record may have no time relation to the incident that led the patient to undergo surgery, since there was an undefined interval between the time she was seen in the Out Patient Department and in the ward. The history tells us that eleven years before entry she had a child and that at the time of entry she was only twenty-seven. So she must have been married at fifteen, and her husband died at about the time the infant was born. She went four years without the possibility of pregnancy and then remarried. Seven years elapsed during which she presumably tried for a child but did not secure one. These data lead one to suspect an inflammatory process in the genital tract. However, I should like to point out that

*Whitehill, M. R., Longcope, W. T., and Williams, R. Occurrence and significance of myocardial failure in acute hemorrhagic nephritis. *Bull. Johns Hopkins Hosp.* 64:83-113, 1939.

it is becoming increasingly important to consider the male partner in any question of sterility. There is no mention of the husband here.

The urinary tract reveals the possibility of disease. She had nocturia two or three times. The recorded urine probably was not a catheterized specimen and therefore the findings are not entirely reliable. But it is of some significance that there were occasional red cells, 7 white cells and 15 epithelial cells per high-power field. This case reminds me of a girl who had abdominal pain, with little in the line of urinary symptoms. Palpation revealed a slightly tender mass in the left vault the size of an English walnut or perhaps larger; x-ray studies revealed a sac full of stones. She was cystoscoped and a slight slit made in the left ureter produced twenty-seven stones. She had a ureterocele at the base of the ureter where it joined the bladder. That could be the case here.

The pelvic examination in the Out Patient Department was undoubtedly made by a different examiner from the one on the ward. Therefore the 4-cm. tender mass felt by the former and the orange-sized mass felt by the latter could be the same. One examination was made when the patient was in pain, and the other when she was not. One examination was perhaps made by a house-officer, and the other by a visiting man. I cannot be sure but I should like to think for the purpose of what I am going to say later on that there was a change in size in the mass. The leukorrhea in relation to these episodes of pain and the fact that she had a profuse vaginal discharge are rather pertinent even if the cervical smear and culture were negative. As you all know, in the acute stage of a Neisserian infection of the adnexa, culture or smear may fail to show organisms.

The situation before admission to the ward certainly sounds like pelvic inflammatory disease, probably bilateral, with almost certainly a right salpingitis.

We learn from the history that the menarche started at fourteen and that the periods were always regular, with a twenty-eight-day cycle, and lasted three days, with no pain. The last catamenia began five days before the patient entered the hospital.

Since she had been having abdominal pain for at least a week before entry, it must have continued throughout the menstrual period. The fact that the patient had had this period allows me to rule out all complications of pregnancy — ectopic gestation, early abortion and all that sort of thing.

Tenderness on the right side of the rectum suggests diseases of the gastrointestinal tract. I believe one should mention in the differential diagnosis appendicitis, appendiceal abscess, mucocele and Meckel's diverticulum. Another possibility is dermoid cyst, of which we see ten or twelve cases a year in this hospital. Many are unilateral. The bilateral ones are frequently picked up only by pelvic examination, or demonstrated by x-ray, especially if they have teeth in them. Another possibility that should be considered but that can be ruled out by the menstrual history is a ruptured corpus hemorrhagicum. If this attack had occurred midway in the cycle, between the twelfth and twentieth days, such a diagnosis would have to be thought of. The patient could have a persistent corpus luteum — a frequent cause of sterility.

It is obviously impossible to make an exact diagnosis on the data presented. I shall make a diagnosis of pelvic inflammatory disease, with possibly a twist of a hydrosalpinx.

Clinical Diagnosis

Pelvic inflammatory disease.

Dr. Simmons's Diagnoses

Pelvic inflammatory disease, bilateral.
Right hydrosalpinx, with torsion?

Anatomical Diagnosis

Dermoid cyst of ovary.

Pathological Discussion

Dr. Tracy B. Mallory: When this patient was explored a large yellow cystic mass was found in the right ovary. Both tubes were entirely normal, and so was the appendix. The ovarian mass was removed and proved to be a dermoid cyst full of cheesy material and hair; it contained no teeth, bone or any structures that would have been shown by x-ray examination. Nothing was discovered to account for the acute attack of pain that brought her into the hospital on the last occasion. There was no twisted pedicle or any other lesion to explain why this cyst, which evidently had been present for some years, should have suddenly produced symptoms.

Dr. Simmons: Was the mass the reason for operation?

Dr. Mallory: Yes; the preoperative diagnosis was the same as yours — pelvic inflammatory disease.

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NEW AGENTS IN THE TREATMENT OF INFECTIOUS DISEASES

The search for new weapons is a part of modern warfare, and there is no denying the fact that the development of new weapons to aid in the defeat of bacterial infections is well under way. Every physician is familiar with the phenomenal results that have been achieved from the use of the sulfonamides, and now other agents are being discovered, that may be useful in the treatment of infections that fail to respond to the sulfonamides. Among those under investigation at present are the so-called "antibiotic" agents—that is, substances that destroy or so modify biotin that it cannot be used by bacteria for their normal growth.

It has been known for many years that certain bacteria, such as *Pseudomonas pyocyaneus*, elaborate substances that are inhibitory as well as lethal to bacteria. Fleming,[1] in 1929, described a soluble substance, "penicillin," which he obtained from the growth of *Penicillium notatum*, that inhibited the growth of gram-positive organisms in vitro. It was nontoxic to animals when given in relatively large quantities, and it was used by him for the local treatment of ocular infections.

A few years later Dubos and Avery[2] described an enzyme that was obtained from the growth of a bacillus obtained from soil and that was capable of removing and destroying the capsular material of the Type 3 pneumococcus. Other enzymes were derived from bacteria that would act the same way with several other types of pneumococci. Later, Dubos[3] isolated a substance from another species of soil bacillus, *Bacillus brevis*; it was called "tyrothricin." This material is bactericidal for gram-positive organisms and can be separated into two fractions—"gramicidin" and "tyrocidine." Other antibiotic agents have been described recently and include "glyotoxin," "actinomysin," "citrinin" and "aspergillin." Of all these agents, tyrothricin and penicillin have been studied most intensively. In a recent number of *War Medicine*, Rammelkamp[4] summarizes the results that he obtained with tyrothricin in the treatment of infections. Reports on the use of penicillin are beginning to appear from England (Florey and his associates[5]) and from the United States (Dawson and his colleagues[6, 7]).

It is now clear that tyrothricin can be used locally for the treatment of ulcers of the skin, of wounds of the mastoid process and of empyema due to infection with staphylococci, streptococci and pneumococci. Since the material is relatively insoluble except in alcoholic solution and since it does not penetrate the tissues following local application, its use must be confined to the topical treatment of infections. It cannot be given intravenously because of its toxic reactions; there is, however, no evidence that the material is absorbed from local areas of infection since no signs of intoxication follow its topical use. Further studies

on the prophylaxis and treatment of wound infections are needed.

Although penicillin has been known since 1929, it is only recently that there has been a revival of interest in the material as a therapeutic agent in the treatment of infections. The field of application of this important substance is now being explored. Florey and his associates[5] have reported favorable results in a small group of cases of staphylococcal sepsis, and these observations have been confirmed by others. Penicillin has the advantage that it can be given intravenously without causing any reactions and without any sign of intoxication. It is rapidly excreted in the urine and can be recovered from that source in biologically active form. With the known methods of production, however, it is exceedingly difficult to obtain sufficient material to test its efficiency in various infections. Preliminary studies indicate that it is most effective in gram-positive infections, such as those caused by *Staphylococcus aureus*, *Streptococcus haemolyticus* and the pneumococci. Unfortunately, bacterial endocarditis due to *Streptococcus viridans* has not been favorably influenced by penicillin.

It is plain, then, that several new antibiotic agents are now being studied intensively and that it may be possible in the future to add them to the now-existing powerful agents for combating infection.

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ANCIENT OF DAYS

Just as the ancients believed that the heavens sped past them while they on earth stood still, so each of us, as an individual, is prone to think of himself as immutable, unchanging, while all about him goes on its course, ripening and aging and disappearing. Then, like a panic, comes a sudden appreciation of the fact that he has not been watching a procession but has been himself a part of it; that he may have little after all on which to congratulate himself when he notices a friend, paunchy and bald; that his own step has become more sedate, his knees stiffer; that he finds fewer fences of a proper height to vault.

This change is something to view with equanimity if we have kept any of the talents of our earlier years from under the bushel. The lessons to be remembered are that adolescence prolonged into middle age is sometimes silly; that the scars which time inflicts are apt to slow down the machine and necessitate its direction into less swift streams of traffic; that we must use our heads to save our heels; and so on. It might be accepted as something close to an axiom that everyone who lives long enough grows old in time.

Plenty of attempts have been made to rationalize the whole business of, shall we say, maturing, despite or on account of its perfectly obvious inevitability.

> Grow old along with me,
> The best is yet to be

is a typical, if somewhat dubious, example. Pitkin's *Life Begins at Forty* is a serious attempt to reconcile to that roaring decade the young man about to enter it.

The mistake that we see too often is that of making no provision for a change in tempo, of assuming that we are going on engaging in the same occupation in the same manner until we drop in the traces or arrive at that questionable state of existence known as retirement. What is happening now to our retired colleagues, no doubt to the delight of most of them, is that they are being taken from the shelf, dusted off and shaken clear of moth crystals, and put gently back to work.

It is the spirit that must be kept young while the activities are tempered to the accumulating dec-

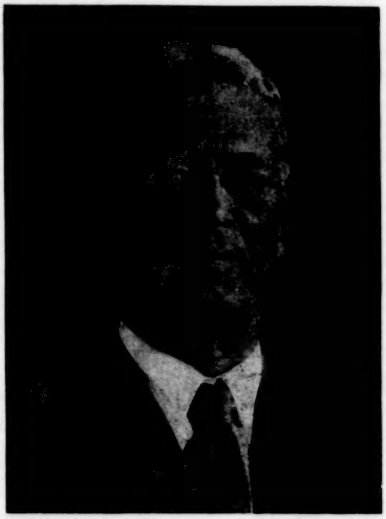
ades, and the expanding resources of the individual's experience are made available. Samuel Johnson referred to the necessity of keeping his friendships in repair. Cato studied and, we are told, learned Greek at eighty. In that memorable story, "The Miracle of Purun Bhagat," Kipling depicts the unfolding, the development and the fulfilment of a fruitful life — twenty years a youth, twenty years a fighter, twenty years a statesman and then the begging bowl and the evening of life devoted to contemplation and the eventual service of mankind in the high Himalayas.

CHARLES SHOREY BUTLER

1870–1943

It is with deep regret that the *Journal* records the death of the able and highly esteemed treasurer of the Massachusetts Medical Society, who died on February 23, after an illness of several months.

Dr. Butler was born in Boston on July 6, 1870, the son of Charles Shorey Butler and Elizabeth Nancy Cummings. He graduated from Harvard College in 1893 and from the Harvard Medical School in 1897. After an internship at the Massachusetts General Hospital he entered private practice, served on the staff of one of the Boston hospitals and taught anatomy at Harvard. Quite early in his medical life he became interested in military medicine and served for seven years as assistant surgeon in the Massachusetts Volunteer Militia. At the time of his resignation he was a captain and assistant surgeon in the 8th Infantry Regiment. In 1915 he became a surgeon in the French Army, for which he was decorated by the French Government, having been made a chevalier of the Legion of Honor. On his return to this country he was commissioned captain in the Medical Reserve Corps of the United States Army and examined candidates for the Air Corps.



After several years Dr. Butler retired from active practice and teaching but continued to have a keen interest in the medical profession, in military medical work and particularly in strengthening preparedness among physicians in civil life. He also retained his interest in the Medical Reserve Corps, in which he held the rank of lieutenant colonel.

Dr. Butler had an interest in finance and financial affairs; he liked to study the reports of corporations and he became a trustee of several estates. As a result of his business interests he was selected for the office of treasurer of the Massachusetts Medical Society, and under his guidance the financial standing of the Society steadily improved. He bought and sold wisely, and his annual reports were received with applause. It is difficult for a medical society to find the right man for treasurer, but Dr. Butler proved his worth over and over again and will be difficult to replace.

Modest and self-effacing, his capabilities were sometimes hidden, but to those who knew him and worked with him his courage and conscientiousness were ever apparent. He strove constantly to maintain the high ideals of the Massachusetts Medical Society, and his wise counsel will be greatly missed and long remembered by his colleagues.

MEDICAL EPONYM

Strümpel-Marie Disease

Adolph Strümpel (1853–1925) in the second volume of the first edition of his *Lehrbuch* (Leipzig, 1884, page 152) described this peculiar form of chronic arthritis. A portion of the translation follows:

> Those forms may here be mentioned in passing as a remarkable and, as it seems to us, a distinct disease in which there results a gradual and painless complete ankylosis of the vertebral column and hip joints so that the head, the trunk and the thighs are firmly united to each other and become completely stiff, while all the other joints retain their normal mobility. It is apparent that a characteristic modification of the posture and gait must occur as a result. We have seen two quite similar cases of this peculiar disease.

He discusses the entity in more detail in an article, "Bemerkung über die chronische ankylosirende Entzündung der Wirbelsaüle und der Hüftgelenke. [A Note on Chronic Ankylosing Inflammation of the Vertebral Column and Hip Joints]." It was published in the *Deutsche Zeitschrift für Nervenheilkunde* (**11**: 338–342, 1897) as a comment on the preceding article on the same subject by Bechterew.

Pierre Marie (b. 1853) wrote "Sur la spondylose rhizomélique [Rhizomelic Spondylosis]" in the *Revue de médecine* (**18**: 285–315, 1898). A portion of the translation follows:

> In the session of February 11 of this year, I presented to the Société médicale des Hopitaux two patients afflicted with a disease whose symptoms, identical in both cases, seemed to me to be sufficiently interesting to be brought to the attention of clinicians. In this preliminary discussion, I indicated the principal characters of this disease entity and particularly stressed the extremely marked rigidity of the spine and the more or less complete ankylosis of the coxofemoral and scapulohumeral joints. Calling attention to the fact that the articulations of the roots of the extremities were affected with this kind of spinal rigidity, I proposed to designate it by the name *rhizomelic spondylosis*. . . .

After a careful review of the facts observed in his cases, he concludes:

> It seems to me that it is permissible for clinicians to contrast deforming polyarthritis affecting the small joints of the extremities (acromelic deforming polyarthritis) with the ankylosing process that attacks primarily the spine and the joints at the roots or attachments of the extremities (rhizomelic spondylosis).

R. W. B.

MISCELLANY

ARMY-NAVY "E" AWARD TO SHARP AND DOHME, INCORPORATED

Sharp and Dohme, pioneers in the development of dried blood plasma, and producers in their laboratories in Philadelphia and nearby Glenolden not only of plasma but of many other disease-preventing, pain-relieving and life-saving medical supplies for the armed forces, were awarded the Army-Navy "E" for excellence in production on Wednesday, February 10. Since both pharmaceutical and biological laboratories received the award, two ceremonies were held. At each, the "E" pennant was presented by Brigadier General Hugh J. Morgan, chief consultant in medicine, Office of the Surgeon General, United States Army. The pennants were received on behalf of the company by Mr. J. S. Zinsser, the president.

NOTE

Dr. E. B. Astwood and Dr. E. W. Dempsey of the Harvard Medical School have been appointed managing editor and associate managing editor, respectively, of *Endocrinology*. They will have the collaboration of a newly established editorial board consisting of Drs. J. S. L. Browne, E. T. Engle, C. G. Hartman, E. C. Kendall, F. C. Koch, C. N. H. Long and H. B. van Dyke.

BOOK REVIEW

The Ophthalmic Formulary. Compiled by G. Griffin Lewis, M.D. 12°, cloth, 167 pp. Springfield, Illinois: Charles C Thomas, 1942. $3.50.

In this volume the author has gathered 115 pages of ophthalmic prescriptions catalogued with reference to the eye diseases treated, and has added 27 pages of ophthalmic materia medica, 8 pages of index and 12 blank pages for notes.

Historically, just as the interest of the reader centers around the formulas set down in the *Ebers Papyrus* for treatment of the Egyptian ophthalmias, so also does the interest of the reader follow the empirical therapy practiced concurrently by each of the prescription authors of the present volume.

Practically, whether the reader of this volume be a general practitioner or an ophthalmologist, he already recognizes that therapy of today is departing from the field of the empirical and seeking a surer footing in the field of the etiologic and the chemical. Topical and empirical therapy in ophthalmology is nowadays deferring to more effective treatment: retinal detachment is referred at once to the experienced ophthalmic surgeon, and diabetic retinitis to the competent internist, and the exogenous and endogenous ophthalmic infections are discussed with and frequently treated by the chemotherapist.

The prospective buyer will purchase this volume to satisfy his curiosity about the therapeutic approach of his contemporary and departed colleagues, but he will not use it for his vade mecum in practice.